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THE IMPORTANCE OF NUTRITION IN INFECTION AND ALLERGY

GRANVILLE F. KNIGHT, M.D., F.A.C.A.
Santa Barbara, California

IT IS difficult to evaluate the role of nutrition in the prevention and treatment of allergic and infectious states. The results of animal experiments are often contradictory and clinical observations difficult to interpret. Nevertheless, a broad relationship does exist.

Cod liver oil and sunshine were used to heal rickets long before vitamin D was known, and the usefulness of the former in the treatment of tuberculosis has recently been reemphasized. Lime juice was not withheld from men dying of scurvy because its action was not understood.

In this modern age we must apply common sense to the problem while awaiting laboratory confirmation of empirically useful methods of treatment. The thesis presented here is based on theoretical, clinical and experimental observations. Most important of all, it works in practice—and that is the acid test.

A healthy body is an efficient chemical factory. Given the right raw materials and a good heredity it should be capable, except for accidents, of developing an efficient endocrine and nervous system, strong bones, muscles and sinews, healthy gums, hard teeth, and good resistance against most invasive bacteria, viruses, and other environmental impacts. Unfortunately, every physician knows that today such is far from being the case. We are dealing with many nutritional cripples. Inadequate food intake over several generations may help to explain not only the widespread incidence of allergy and dental caries, but the frequency of many other degenerative conditions as well.

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Dr. Knight is Past President of the American Academy of Nutrition and Attending Physician at Santa Barbara College Hospital.

PRIMARY NUTRIENTS

Not many decades ago, the problem of nutrition seemed relatively simple. At the turn of the century research was mainly concentrated on proteins, carbohydrates and fats, together with iron, calcium, and phosphorus.

Just before the First World War it was shown that unrefined foods contained substances other than the above that were necessary to sustain life. The discovery of vitamins led to the conception that numerous afflictions might be due to deficiencies rather than to toxins or infections. Since then, the discovery, isolation and even synthesis of these compounds has proceeded rapidly. Unfortunately, the practical application of this knowledge has not kept pace with the facts.

VITAMINS

Vitamins may be defined as organic catalysts that are necessary in the daily diet of man or animals for normal growth and for the maintenance of health and life. They are known to be an indispensable part of certain enzyme systems.

The vitamin A group consists of several fractions and a number of carotenes (pro vitamin A) which are converted to A by the intestinal mucosa. Deficiency results in xerophthalmia, mucous membrane metaplasia to squamous type and dermal hyperkeratosis. Reduced resistance to bacterial invasion is one result of metaplasia.

The vitamin B complex has now been split into many components with as many as fifteen fractions suspected. The main ones are: thiamin, riboflavin, pyridoxine, cyanocobalamin or B_{12}, nicotinamide, pantothenic acid, biotin, choline, inositol, *p*-aminobenzoic acid, folic acid and possibly B_{15} or pangamic acid. Since their functions are fairly well known, they will not be discussed. Only recently was evidence available to prove the necessity of pyridoxine in human nutrition.[1] This was fortuitous. Babies fed on a certain heat-processed milk substitute developed convulsions. The addition of pyridoxine relieved the condition. This product now contains adequate amounts of this vitamin.

Vitamin C is essential for capillary strength and for the formation of adequate collagen and connective tissue ground substance.

Vitamin D is composed of several fractions. D_2 is irradiated ergosterol; D_3 is 7-dehydrocholesterol in irradiated form. The latter is the natural vitamin found in fish liver oils and the skin. It is considerably more active therapeutically than D_2 and possibly less toxic.[2]

The Vitamin E group, which includes several tocopherols, acts as an antioxidant, and is important as an antisterility factor. In experimental animals it prevents muscular dystrophy. If cattle are fed a vitamin E deficient ration for one year, one-half of the group will die of heart failure within three years.[3] Electrocardiographic studies of deficient animals have revealed definite indications of cardiac abnormalities.[4]

Essential unsaturated fatty acids such a linoleic, linolenic, arachidonic

and clupanodonic (formerly called vitamin F), while not true vitamins, are important nutritional factors often lacking in the modern diet. They are partially destroyed during the hydrogenation of fats, and are necessary for growth, a healthy skin, and adequate gonadal function. In addition, they boost resistance to infection by their pyridoxine synergism.

The vitamin K group is necessary as a blood clotting factor.

The vitamin P group, or citrus bioflavinoids, include hesperidin, citrin and rutin. They decrease capillary fragility and are receiving increasing attention. These substances enhance the activity of ascorbic acid.

Other vitamins will undoubtedly be discovered in the future. The basic fact to remember is that they all exist in *natural, unprocessed foods.*

TRACE MINERALS

The importance of trace minerals for plants and animals has been known for some time. Only recently, except for iodine, has such knowledge been transferred to the body economy of man. These catalysts are a vital part of many enzymes. They are particularly important for adequate function of C and the B-complex.

Zinc seems to be a part of the insulin molecule and cobalt is inseparable from B_{12}. The following minerals in trace amounts are necessary for plants and animals and probably for man: iodine, manganese, cobalt, zinc, molybdenum, boron, magnesium and copper.

CONFUSION REGARDING NUTRITIOUS FOODS

While there is widespread awareness both by physicians and the public of the basic importance of vitamins, as related to preventive medicine and good health, there is much confusion as well.

The enrichment program for white bread, while a tacit admission that white flour is an incomplete food, has lulled the public into a false sense of security. Only a few of the important nutritional substances removed in milling have been replaced.

Aggressive advertising has convinced not only the average housewife, but her offspring as well, that candy bars, cookies, ice cream, sweetened soft drinks, and cereal from guns, supply quick energy that is a *must* for active young bodies. They are not told that starches break down gradually into useful sugars and that *unrefined* starches, proteins and edible fruits supply all the sugars the body needs. These latter foods come complete with vitamins, minerals, and other valuable accessory food factors.

Mothers are not informed that their children's bodies are best equipped to handle sugar at a slow rate from natural foods, rather than a sudden flood of sucrose or glucose; nor are they told that sugar consumption is the most potent cause of dental caries in the 95 per cent of children in this country who do not possess natural immunity to decay.[5] Norman Jolliffe has coined the apt phrase, "empty calories" to describe such foods.

Instead, the average housewife relaxes in the knowledge that the miracle

vitamins which science has discovered may be bought at the drug store to overcome any possible deficiency in the diet. She is led to believe that one capsule a day will make restitution for all the nutrients that have been removed from her children's food. They "can have their cake and eat it, too." Unfortunately, this is not true, and the result is physical degeneration.

We are living in an age of technologic miracles. It is easy to lose sight of basic facts and natural laws, and the penalty may be racial extinction.

The past century has witnessed an industrial revolution which is still going on. With the advent of manufacturing machinery and the motor car, there has been an increasing shift of our population from the farm to the city. Mechanization of agriculture has enabled each farmer to produce food for more individuals than was ever dreamed possible. This move to the cities has necessitated transportation of food to these areas and has stimulated processing to improve the keeping qualities of perishables; in turn, nutritional values have suffered.

Freshly ground whole wheat flour, containing the germ and all parts of the kernel, unless refrigerated, soon becomes rancid from oxidation of the oil, as well as infested with insects. Patent flour keeps indefinitely and inferior grades can be bleached to a uniform whiteness. In processing, the endosperm and coating are removed and sold for cattle feed, or for the production of vitamins. They contain the greater part of the minerals, B complex vitamins, vitamin E, and protein found in the natural grain.

White sugar has taste appeal and needs no preservative. In the past century the annual per capita consumption of this product has increased from seventeen to over 100 pounds. Many people each year actually eat their weight in sugar. It has been conservatively estimated that more than half the caloric intake in the average American diet is in the form of white bread and white sugar.[5] Canned foods, through heat sterilization, lose many of their nutritive qualities. Frozen foods are relatively unchanged. Vegetables and fruits are usually picked before complete ripening and lose vitamins in transportation. Cold storage meat is not the same as fresh. The increasing use of hydrogenated fats in our dietary reduces the intake of essential unsaturated fatty acids. This may be related to vascular degeneration. The pasteurization of milk, while essential in most areas for the prevention of disease, probably renders this fluid less nutritious. There is partial destruction of vitamins, inactivation of enzymes, denaturation of the protein, and the calcium seems to be less assimilable. Unless *certified* raw milk is available, other foods must supply the difference. Since the majority of modern mothers are either unwilling or unable to breast-feed their infants, many of our children are off to a poor start. As a rule, infants are placed on a formula of powdered milk and sugar, which may be lacking in important nutritional factors.

Most consumers dislike powdered or cold storage eggs. Their taste tells them such products are inferior. Present day efficiency has resulted

in individual cages for laying hens; not only are such birds subjected to enforced celibacy, but they are prevented from exercising any choice in food and do not have access to grass and weeds that might round out their man-made diet. Naturally, if the feed is inadequate, the eggs reflect it. Paper-thin shells, so common these days, are obviously low in calcium.

PRESERVATIVES AND ADULTERANTS

The problem of preservatives and adulterants in foods is a long story and can only be mentioned in passing. After being used for many years to bleach flour, agene (NCl_3) was recently found to produce denaturation of the protein sufficient to cause running fits in dogs.[6] The effects on human metabolism have not been determined. Nitrogen dioxide, of unproven toxicity, is now being used as a substitute. The chronic toxicity of chemical preservatives in foods, together with the newer wetting agents of the polyoxyethylene group, still await adequate investigation; and yet their use in our foods is permitted.[7]

PROTEINS

Growth, reproduction, antibody formation, enzyme function, and repair of body tissue require an adequate protein intake. The essential amino acids, which constitute protein building blocks, must be present in sufficient and balanced amounts *at the same time* in order to be utilized. An incomplete protein ration, lacking in only one essential amino acid, will not sustain the life of rats. Addition of the missing amino acid is effective only if fed within one hour of the balance of the food.[8]

This is a valid argument for physicians to advocate the use of complete proteins such as meat, fish, milk, eggs and cheese. Since vegetable proteins usually are deficient in one or more of the essential amino acids, a pure vegetarian diet must be scientifically balanced in order to be adequate.[8]

Stress situations and prolonged bed rest increase the need for protein. The latter produces muscular wasting and a negative nitrogen balance. Thus early ambulation following surgery and other traumatic conditions, plus a high protein intake, are logical procedures.

And yet, an extremely high protein intake is not only wasteful, but may strain eliminative processes in some patients. If digestion and elimination are defective, toxic amines from the colon may produce severe disturbances. One wonders how certain primitive tribes not only subsist, but develop and maintain superb physiques and perfect teeth on such monotonous fare as black rye bread, turnip soup, vegetables in season, roots, nuts and other foods seldom seen on American tables, with animal protein once or twice a week as a luxury item. Science should answer this question by confirming, if possible, the observations of Dr. Price.[9] He found such diets (while vastly different) to be unusually high in vitamins, calcium, phosphorus, magnesium and trace minerals.

ENZYMES AND BIOLOGIC ANTAGONISTS

Life processes in each body cell are the result of chemical reactions sparked or catalyzed by enzymes. There is evidence that genes are enzymes with specific functions. Thousands of enzymatic reactions occur simultaneouly in each cell and influence the rate and degree of activity of each other. Such complexity baffles the investigator and is indeed awe-inspiring.

Enzymes contain amino acids, vitamins and minerals. Effective function depends not only upon the presence of the necessary raw materials but upon the absence of interfering substances.

Obviously, nutritional deficiency will decrease the function of these catalysts. So will the presence of a variety of chemicals acting as anti-enzymes. Cyanide inactivates the mineral component; others, such as sulfanilamide, because of an almost identical chemical structure, substitute for the necessary vitamin fraction. Most useful and harmful chemicals act in this way. For example, sedatives selectively block oxidative enzymes in nerve tissues, as do the anesthetics. The potent nerve gases and closely related organic phosphate group of insecticides, such as TEPP and parathion, rapidly inactivate cholinesterase. DDT and similar insecticides inactivate cytochrome oxidase, but their main mode of action is still unknown. Other drugs, such as aspirin and sedatives increase the excretion of vitamin C. High fever apparently destroys ascorbic acid quite rapidly.[10]

Hundreds of synthetic antimetabolites are now being synthesized in our research laboratories with the hope that one or more will be found to inactivate enzymes essential for neoplastic growth, while not affecting those vital for normal cells.[10] This approach holds much promise, but ignores basic causes.

Modern living has exposed mankind to an increasing number of chemicals with antimetabolic activity. These include tobacco, alcohol, industrial wastes in the air we breathe, chemical softeners, coal tar dyes, estrogenic hormones, antibiotic and insecticide residues in our foods, antibiotics used in treatment, pain killers, sedatives and other therapeutic drugs; pesticide residues of DDT, chlordane, lindane, methoxycholor and others widely advocated for use in our homes and public buildings;[11,12,13,14,15] and now in many cities the calculated addition of fluorides to our drinking water presents another serious hazard.[17,18,19] Physicians, dentists and the public should learn the facts about this dubious experiment.

Stilbestrol has been advocated for several years to increase the market weight of chickens. In addition, this potent chemical is now added to the feed consumed by more than half our beef cattle. A recent report indicates that the residue in the meat, while minute, is ten times the amount necessary to induce carcinoma of the uterus in small experimental animals.[16]

FLUORIDES

At this point it is pertinent to comment on a strange phenomenon that is adding one more toxic chemical to the load already borne by our bodies—namely, the drive by the Public Health Service to persuade cities to fluoridate their water supplies. This action merits discussion not only because of the potential health hazard involved, but because of the not so obvious threat to the private practice of medicine and dentistry. A concerted and effective propaganda campaign has pressured most of our major medical and dental societies into endorsement of fluoridation without adequate knowledge or consideration of the whole subject.

The Public Health Service argues that fluoridation is a means of reducing dental caries and, being a preventive measure, lies within its sphere of influence—as does the chlorination of our water supply. Nevertheless, there is a vast difference—and one must not be confused by semantics. Chlorination *treats the water* to destroy harmful bacteria (chiefly typhoid) that might cause epidemics; fluoridation *treats the consumer* by inducing changes in the bodies of those drinking such chemically treated water. What is more, fluoridation exposes all those using a communal water supply to an unnecessary hazard. It is common knowledge that adults will derive no benefit from fluoridated water, and there is increasing evidence that some of them will be harmed.

One of the first observable signs of fluoride toxicity in children is hardening of the dental enamel, which shows as chalky-white patches that later turn brown, gray or black. After sufficiently prolonged exposure to fluorides (fifteen to twenty-five years) some individuals may develop disabling osteosclerosis or osteoporosis, pulp stones in their teeth, pyorrhea, and other manifestations of systemic fluorosis.[17]

Speaking solely as an individual, I will note some of the objections to fluoridation with the hope that those unfamiliar with the subject will seek more information. The vitality of our nation as well as our professional freedom may well depend upon the outcome of this controversy. If the principle involved is accepted, what is to stop the Public Health Service from adding Isoniazid® to our water for the prevention of tuberculosis? Or any other medication that they may deem advisable for the prevention or treatment of disease?

Exner[18] has published a logical and comprehensive critique of the whole question. He considers fluoridation to be immoral, adulteration of the water supply, and mass medication. His studies indicate that the statistics purporting to show a significant reduction of tooth decay in those children drinking water artificially fluoridated at a concentration of one part per million are unreliable and conflicting. He believes there is no adequate evidence in support of claims that toxic effects do not occur.

Klerer,[19] in a recent exhaustive and well documented article reaches the same conclusions and stresses dental fluorosis and bone changes in

humans living in areas where the water supply is high in natural fluorides. He is convinced that artificial fluoridation is extremely hazardous.

Sodium fluoride is a very toxic chemical that accumulates in the body *at any concentration.* This has been proven by Wallace-Durbin[20] who used radioactive tracer studies for this purpose. Sodium fluoride inhibits most enzyme systems. It is a general protoplasmic poison and reacts with bones and tooth enamel to produce irreversible changes. Contrary to popular opinion it is not a trace element necessary for animal nutrition.[21]

The dose of any drug dissolved in the water supply obviously cannot be controlled. Even proponents admit that 15 to 20 per cent of children drinking such water will develop mottled teeth.[22] Individual susceptibility may be expected to vary with inheritance, the amount and hardness of the water consumed, the concentration of fluoride, the nutritional status, kidney function, allergy and other factors.

The experiences of Waldbott have been illuminating. He has not only studied the literature extensively, but has discovered clinical evidence of fluoride toxicity. He has personally observed and reported serious illness resulting from the consumption of artificially fluoridated water.[23,24] From the literature[25,26] he cites two fatal cases exhibiting marked generalized fluorosis. The latter drank naturally fluoridated water at a concentration of about 2 ppm. Kidney disease may have been a predisposing factor.

Forman[27] has effectively stated the practical and theoretical objections to artificial fluoridation.

Expert testimony heard before Congressional committees[28,29] presents an excellent picture of both sides of the question.

One may summarize by stating that artificial fluoridation is illogical and an invasion of personal rights. It is premature and based upon questionable statistical evidence. It is expensive, and the dosage uncontrollable. The indiscriminate treatment of all members of a community by the addition of a potent chemical to the water supply without regard for, or knowledge of, the state of health of each individual, is dangerous and totalitarian in nature. As Exner says, "We are entitled to pure water from the tap—not medicine or soup."

Fluorides can be administered to children, whose parents request it, in accurate doses and at low cost in the form of drops or tablets. Why fluoridation? Almost all cases of dental caries can be controlled by the avoidance of sugar and refined carbohydrates together with an adequate diet.

PREPARATION OF FOOD

Even excellent food of high nutritional quality can be and often is ruined in the kitchen.

Vitamin C is very unstable in the presence of oxygen. Vegetables and fruits begin to lose it right after harvest. Ascorbic acid is very

vulnerable to heat, particularly in an alkaline medium. Finely-shredded cole slaw will lose most of its vitamin C content in one hour.

The B-Complex vitamins are water soluble. When much cooking water is used and then discarded, more than half of the B group may go with it. That makes as much sense as throwing away fluid coffee and eating the grounds. Vegetables should be steamed or cooked in a small amount of water, and the residual cooking water, if any, consumed with them or added to soup or tomato juice. This method also conserves the valuable minerals.

SOIL CONSERVATION

In the exploitation of this country's vast natural resources, man has been criminally careless of the soil. Until recently, there was always virgin land to the west, and many farms were abandoned to the weather once the original fertility was used up. Indiscriminate destruction of our forest watersheds has led to recurrent floods and droughts, and has hastened the movement of topsoil to the sea. The deep-rooted grasses and plants of the western plains have been replaced by less hardy wheat and corn, unable to live through a dry cycle. The wind has dissipated hundreds of thousands of tons of fertile soil as a result. So now we have reached the stage when many areas have lost the few inches of precious topsoil that mean the difference between life and death.

In recent decades, the demands of war and the spur of price supports have induced farmers to produce bumper crops in quick succession without replenishing the soil by means of crop rotation and the addition of organic material. Commercial fertilizer has not supplied the needed organic matter nor the important trace elements.

The newer pesticides have upset the balance of nature, killing natural insect enemies as well as the insects themselves and by contamination of the soil may have upset the teeming billions of soil organisms necesary to release plant nutrients and to produce natural antibiotics.

The end result of all these factors is a steadily declining protein content of our grains, grasses and vegetables, which thus weakened, seem to be increasingly less resistant to the insect hordes.[30] Deficient soils produce deficient plants, and poor fodder does not foster strong animals. And so we come full circle to man who must now pay for his blindness: *For we are what we eat.*

EVIDENCE OF NUTRITIONAL DEFICIENCY

There has been in the past considerable argument concerning the incidence of nutritional deficiency in the United States. It has been difficult for many to accept the idea that in "the best fed nation in the world" such a condition might be widespread. However, our high draft rejection rate and our poor showing in the recent Olympic Games leave

little room for doubt. A study of primitive races in their native environments is quite illuminating.

The late Weston A. Price, a dentist with original ideas, through extensive travels discovered that natives in all parts of the world on their natural tribal diets were not afflicted with dental caries, and enjoyed excellent general health. Contact with civilization and the resultant consumption of white flour, sugar and canned goods produced not only tooth decay, but deformed dental arches in the second generation, together with a marked increase in infectious and degenerative diseases. His book contains numerous photographs dramatically supporting his thesis.[9]

Sir Robert McCarrison, in his classic book "Studies in Deficiency Diseases,"[31] recorded some very interesting experiments. Several varieties of animals were fed diets of autoclaved white rice with occasional supplements. Careful postmortem studies were done. The most significant gross findings in the gastrointestinal tract were dilatation of the stomach, and thinning of the wall, muscular atrophy and distention of the small bowel or colon. Microscopic examination revealed congestion and hemorrhage, atrophy of the muscular coat, degenerative changes in Auerbach's plexus of nerve ganglia, atrophy and inflammation of the mucous membrane and lymphoid structures, fibrosis and lowered resistance to bacterial invasion of the bowel wall (mostly cocci).

Chronic passive congestion of the liver with slight atrophy and necrosis accompanied atrophy of the pancreas which was often extensive. The endocrine glands revealed atrophy of the thyroid, spleen and thymus in contrast to hypertrophy of the adrenals and pituitary. (Hans Selye has since termed this the "Alarm Reaction.") The central nervous system and autonomic ganglia showed degeneration.

In another study, when rats were fed the average diet of the English and Americans, including white flour and sugar, the animals developed sinusitis, otitis media, abscesses, arthritis, pyelonephritis and other infectious and degenerative ailments akin to those afflicting the human race.

The observations of F. M. Pottenger, Jr.[32] substantiate these findings. He noted that raw meat and raw milk produced generations of alert cats in excellent health and full of feline exuberance. The other half of this same litter, when fed on cooked meat and pasteurized milk only, developed osteomalacia, pyorrhea, sinus infections, pneumonia, and a great increase in allergic manifestations, up to 90 per cent of those surviving. Degeneration was so rapid that reproduction was seldom possible beyond the third generation. It took another three generations on raw food to breed the few survivors back to normal.

Morton Biskind, Roger Williams, N. Philip Norman, Tom Spies, Gillman and Gillman, and Jonathan Forman, together with many others have stressed the importance of malnutrition in the production of disease.[32-38]

Surveys conducted by the National Research Council and other groups have shown that only a small percentage of families in this country are consuming a diet meeting the Council's recommendations.[39] The figures of Canadian investigators are similar.

NUTRITION AND INFECTION

The results of animal experimentation to determine the effects of single vitamin deficiencies upon resistance to infection are often contradictory and confusing.[40-43] On the whole, there is evidence that malnutrition *decreases resistance* to bacterial infection, but in some instances *may increase resistance* to the invasion of viruses. Apparently, the virus competes with the body cell for certain essential nutrients and fails to multiply if these are not available in sufficient amounts. However, the opposite is also true, and in clinical practice at least, improved nutrition raises resistance against viruses as well as bacteria. Recently, Axelrod[44] has reported that pantothenic acid, folic acid and pyridoxine are essential for antibody formation in the rat. It has been definitely proven that vitamin A deficiency lowers resistance to bacterial infection in many parts of the body.

Vitamin C deficiency delays solid wound healing. It also interferes with the localization of staphylococcus infections; collagen fails to form and the reticular ground substance is disorganized.[45]

NUTRITION AND ALLERGY

Many asthmatic children and adults develop severe attacks concurrent with upper respiratory infections. An unknown number of cases of chronic allergic rhinitis and intrinsic asthma are thought to be due to bacterial allergy. It is therefore vitally important to reduce the incidence of respiratory infections. The regime to be outlined later is very effective in this respect.

Specific vitamin therapy in allergy has centered mainly around vitamin C. Simon Ruskin[46,47] has reported favorably on the use of calcium ascorbate in the treatment of hay fever. Ethan Allan Brown[48] has also worked along these lines. Results seem to be equivocal but the writer has observed that large doses (1-3 gm) daily of ascorbic acid are useful adjuncts in both allergic and infectious states. Larger amounts may be indicated. Intensive parenteral therapy has been reported to produce dramatic improvement in acute virus infections, including poliomyelitis.[49]

Since most deficiencies are multiple, it would seem of paramount importance to attempt to supply each patient with the optimum amount of all nutrients needed by that individual. Such requirements vary widely depending among other things upon inheritance, past nutritional habits, liver pathology, state of the gastrointestinal tract, including hypochlorhydria and colitis, chronic illnesses, such as allergic states, diabetes, tuberculosis, arthritis and, lastly, emotional disturbances.

Many deficiency states, in addition to an adequate diet, require vitamin supplements in therapeutic amounts. Except for vitamin D, this means ten or more times the estimated minimum daily requirements. Some individuals, perhaps as a result of partial genetic blocks involving enzyme systems,[34] may always need nutritional supplements, since they cannot satisfy abnormally large vitamin needs from food alone. It has been observed that animals once severely deficient require excessively large amounts of vitamins thereafter to keep them in nutritional balance. This is also true for human beings. Give Nature the raw materials and she can often perform wonders.

PERSONAL OBSERVATIONS

In the past fifteen years, recorded observations reveal that between 60 and 90 per cent of all patients coming to my office with allergic, or ear, nose and throat complaints have shown clinical evidence of vitamin B complex deficiency. Diet histories in almost all cases have revealed an excessive intake of refined foods and a paucity of the protective ones. About 20 per cent have shown signs of deficiency in vitamin A. Many have had gingivitis and almost all have had obviously deformed dental arches with a crowded and irregular dentition, in addition to evidence of caries or filled teeth.

Allergic states, recurrent sinus infection, otitis media, tonsillitis and stubborn external otitis responded poorly until dietary correction was made. Vitamin supplements were almost always necessary but not curative in themselves. It is of interest to note that on a good nutritional regime allergic individuals seldom develop new sensitivities.

Before outlining the basic nutritional suggestions made in all cases, one case report will illustrate the problem and the results to be anticipated.

CASE REPORT

A six-year-old girl was brought to the office with a history of repeated tonsillitis and acute otitis media recurring every ten days or two weeks over a two year period. During that time her parents had spent in excess of $2,000.00 for her medical care, most of which represented the purchase of antibiotics. The mother was frantic and worn out by constant nursing care, as well as by worry about her daughter's health.

Except for enlarged, red tonsils, scarred ear drums, a red tongue, hyperkeratotic changes of the skin typical of vitamin A deficiency, numerous fillings in her teeth and a secondary anemia, examination was not remarkable. The child's diet was fairly good (for the mother was conscientious), except for the inclusion of dried cereals, white bread, homogenized milk and a sweet dessert once daily plus several cookies in the afternoon.

Correction of her diet according to the basic regime to be described later, plus the addition of vitamin supplements including A, C, B-complex, unsaturated fatty acids and a multi-vitamin preparation, worked wonders.

One more infection, requiring an antibiotic, occurred twelve days after the first visit. A second, two weeks later, was surmounted without such aid. Since then, her health has shown marked improvement in spite of exposure to virulent infections.

While therapy must be tailored to fit each case, this result is typical of the response to be expected from the application of practical nutritional knowledge. Many more cases could be cited but time does not permit.

RECOMMENDATIONS

The following recommendations with modifications as indicated are made to my patients. These stress the vitamin and mineral rich foods:

1. Avoid white bread and commercial whole wheat bread unless freshly ground and baked. Local bakers will co-operate if assured of a demand; otherwise, home baking is advised. A high protein, hard wheat should be used. The result is not only nutritious but delicious.
2. If available, use *certified* raw milk except for cooking.
3. At first, eliminate sugar in all forms, such as pastries, ice cream, soft drinks, candy, jams, jellies and sugar as such. Later, sweets may be permitted once or twice weekly or at parties.
4. Change from processed cereals to stone ground or steel cut oatmeal and freshly ground whole wheat.
5. Use brown rice instead of white.
6. Bake or boil potatoes and eat the jackets; mashed potato has lost its ascorbic acid.
7. Eat plenty of fish, beef and other high protein foods, including liver, kidneys, sweetbreads, brains and tripe. Animal organs are high in vitamins and trace minerals. Learn to like rare beef, lamb and beef liver. (Cook pork well because of the danger of trichinosis.)
8. Increase the intake of raw fruits and green and yellow vegetables. Vegetables should be steamed and the cooking water, if any, consumed. Vegetables, when possible, should be home grown or free from spray residues. Peel all fruit because of the danger of DDT and other new insecticides. Washing will not remove them.
9. Eat one or two eggs daily and purchase fertile ranch eggs when possible.
10. Serve fruits or cheese for dessert.
11. Take vitamin supplements as directed. In addition to concentrates, yeast, wheat germ and raw liver must usually be consumed to supply a balanced ration of the known and unknown fractions of the B complex group.

In severe deficiencies, poor absorption may necessitate injections of vitamin B complex and/or liver for a few weeks.

Progress is frequently slow, for deficiencies have usually developed over a period of years. Patients should be informed of this, so that they will not become discouraged and revert to their old habits. *Full benefit* of the new routine may not be obtained for six months or a

year, but in obvious B-complex depletion increased appetite and a feeling of well being are often noticeable within a week. Tooth decay in cooperative patients usually may be eliminated.

George Herbert once made the remark, "Whatsoever is the father of disease, an ill diet was its mother." To me, there is no greater satisfaction in the practice of medicine than to have a patient say, "Doctor, I feel ten years younger!"

Any attempt to change ingrained food habits and customs meets with marked resistance. The desire to conform is especially strong in teenagers. This adolescent group, because of rapid growth, is particularly vulnerable to dietary deficiencies and prone to consume large quantities of refined carbohydrates. Psychologic rapport is difficult, for this age group is naturally defiant of all authority. Tact and diplomacy are essential for success.

SUMMARY AND CONCLUSIONS

In spite of an adequate caloric intake, there is widespread evidence of nutritional deficiency in the United States. This statement is supported both by reliable statistics and by personal observations.

Theoretically, malnutrition may be the result of our mechanical age. Population moves from farms to cities have created problems of food preservation and transport. Food processing has decreased the vitamin, mineral and protein values of many staple foods, already low because many such foods were raised on depleted soil.

Chemical additives and contaminants in our foods, air and water may seriously interfere with vital chemical reactions in the body, thus predisposing to or inducing the development of disease. The campaign to fluoridate domestic water supplies adds one more chemical to the vast number which the body must detoxicate.

The high intake of refined carbohydrates so typical of most diets, together with poor food selection, wasteful cooking methods and other stresses, gradually lead to malnutrition in many individuals. Adequate nutrition is of the greatest importance for the production and maintenance of healthy tissues. Deficiency states lower resistance to infection and indirectly predispose to allergic states, perhaps over several generations.

Vitamin supplements are not enough. We must produce food not primarily for quantity, but for quality. Better food as the result of improved farming practices, uncontaminated by insecticides and other chemicals, must be combined with new food habits if a healthy race is to be preserved. Tooth decay in 90 per cent of cooperative individuals can be controlled by means of a good diet and the avoidance of sugar. It is probable that the answer to our degenerative diseases lies not in more medical facilities, vaccines or wonder drugs, but in the application of nutritional knowledge to prevention and treatment. The global implications are obvious.

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The most important discoveries of the laws, methods and progress of Nature have nearly always sprung from the examination of the smallest objects which she contains.—Ascribed to J. B. LAMARCK, in *The World of Mathematics* by JAMES R. NEWMAN.

THE USE OF AN ANTICHOLINERGIC DRUG IN THE TREATMENT OF ASTHMA

D. EDWARD FRANK, M.D., F.A.C.A.
Sun Valley, California, and

WALTER R. MacLAREN, M.D., F.A.C.A.
Pasadena, California

THE QUEST for an ideal therapeutic agent for the treatment of chronic asthma continues its march in all directions. An early description of bronchial asthma as a condition of pathologic vagotonia[3] emphasized the vagal innervation of the bronchial mucosa and musculature. Many therapeutic agents used in asthma relieve bronchospasm, with a relative neglect of the obstructive secretions, or sometimes actually aggravate the problem of secretion. Adrenergic drugs, such as epinephrine, are excellent for relief of bronchospasm, particularly in the paroxysmal attack of asthma, but may be only partially effective in the chronic asthmatic with inspissated plugs. Anticholinergic[1,4,7] drugs may act similarly by relieving bronchospasm through their action as parasympathetic blocking agents, but some of these drugs will produce marked drying of the secretions and thereby aggravate the situation. At present, the search continues for liquefying agents, wetting agents like Alevaire[5,9] or enzyme digestants like trypsin[10]. The ideal agent should have the properties of relieving spasm and liquefying secretions; perhaps a mixture of drugs with these properties will be found most satisfactory.

Margolin, et al.,[7] reported on a new parasympathetic blocking agent in 1951, designated as Prantal.® They showed this quaternary ammonium derivative (N, N dimethyl-4-piperidyline 1, 1 diphenlymethane methyl sulphate), administered orally, prevented bronchospasm and death in guinea pigs which would ordinarily result from the intravenous injection of acetylcholine. There was a high ratio of safety between toxicity and pharmacologically effective doses. Segal and his group[12] reported on the successful use of Pamine,® another anticholinergic agent, administered by them as an aerosol. In this manner it "appeared effective in relieving the bronchospasm and dyspnea of an asthmatic attack." Vickers[13] has reported on the successful use of Prantal, intramuscularly in doses of 10 to 15 mg for the relief of the acute asthmatic paroxysm. This has been amplified by Dann, Brown and Kupperman[2] who demonstrated not only the usefulness of this same drug parenterally, but also compared it objectively to injections of ephedrine, aminophyllin and epinephrine, by means of spirometric studies on asthmatic patients, before and after use

From the Department of Medicine, University of Southern California and the Allergy Clinic, Los Angeles County General Hospital.

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of the drugs. By this method they found that in 25 mg doses it was equal to 0.5 mg epinephrine. Previously we had found Prantal, orally, ineffective in asthma[4], but effective in nasal allergies. We wished further to test the work of Vickers, as well as Dann et al, and also note the

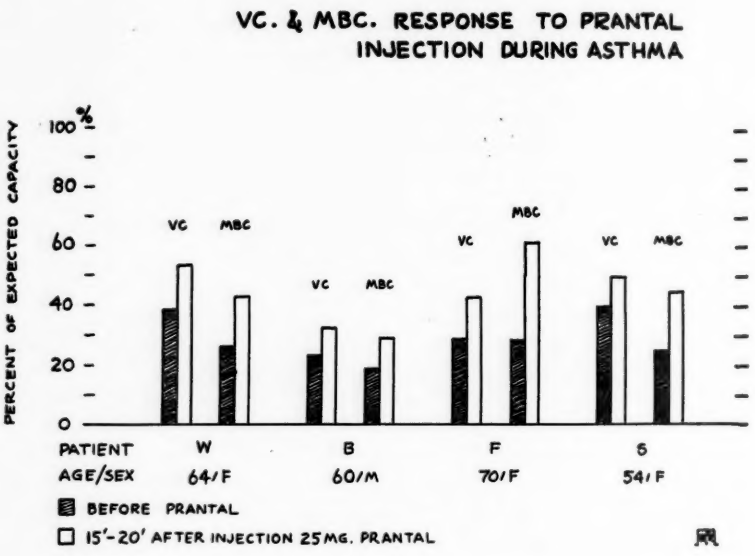

Fig. 1.

effect of this anticholinergic agent parenterally, used on a long term basis in patients with chronic asthma.

The present investigation encompassed four different types of studies: (1) treatment of chronic asthmatic patients in a paroxysm of asthma with the agent subcutaneously; (2) study of a group of persons with chronic asthma in a dyspnea-free state treated with the drug subcutaneously; (3) treatment of chronic asthmatic patients with Prantal* injections on a long term basis; (4) treatment of patients with chronic asthma with high oral doses of this agent on a long term basis. Spirometric studies were done on all patients, consisting of a three-second vital capacity test, plus a maximal breathing capacity test.

PROCEDURE AND RESULTS

Group 1.—Thirty patients who were in an acute paroxysm of asthma received Prantal, subcutaneously, 25 to 35 mg for adults and 10 to 15 mg for children, depending upon the weight of the patient. One-half of the patients were children. Some of these patients were mild, others had severe

*Kindly supplied through the courtesy of the Schering Corporation under a research grant for the conduct of these experiments.

TABLE I. PRANTAL SUBCUTANEOUSLY IN CHRONIC ASTHMATICS IN NON-DYSPNEIC PHASE: SPIROMETRIC STUDY

Case	Degree Asthma	Vital Capacity*			Maximal Breathing Capacity*		
		Before Prantal	After Prantal	Percent Change	Before Prantal	After Prantal	Percent Change
1. AMA		74.8	93.1	16.6	53.2	76.7	44.1
	Mod.	91.6	99.7	8.8	64.7	75.2	16.2
2. BAX	Very	20.5	23.7	15.6	9.8	9.8	0.0
	Severe	37.0	45.4	22.9	13.3	14.8	11.2
3. BEL	Very	26.6	29.9	12.4	18.9	26.0	37.5
	Severe	28.7	34.2	19.1	18.9	18.9	0.0
4. DAV	Mod.	42.8	41.5	− 3.0	38.0	43.6	14.7
	Severe	29.0	43.5	50.0	21.7	26.0	19.8
5. DORF	Mod.	69.8	78.6	12.6	41.3	43.6	5.8
		57.9	50.3	−13.1	39.6	38.2	− 2.0
6. FERR	Mod. Sev.	51.4	51.4	0.0	78.4	58.7	−25.1
7. GOM	Mod. Sev.	65.5	73.0	12.9	83.0	85.6	3.1
8. GONZ	Mod.	59.0	58.6	0.6	55.0	53.0	− 3.6
9. GUER	Mod.	58.3	56.3	− 3.4	78.0	78.0	0.0
	Severe	52.6	58.3	10.8	78.0	86.0	10.2
10. HOPK	Mod. Sev.	42.4	47.4	11.7	34.6	36.7	6.0
11. LAK	Mod.	37.8	57.6	52.4	42.4	52.5	26.1
12. LEW	Mod.	49.2	57.1	16.0	57.0	57.0	0.0
	Severe	65.4	74.5	15.4	36.0	47.5	31.9
13. RAM	Mod.	84.0	86.0	2.3	51.0	60.0	17.6
	Severe	54.0	73.0	53.6	42.0	66.0	57.1
14. WASH		39.4	38.9	− 1.2	19.1	38.4	101.0
	Mod.	50.3	58.8	16.9	31.9	35.1	13.1
		50.5	36.9	−26.9	26.1	31.9	22.2
		38.3	53.4	39.4	25.5	43.4	70.1
15. NEV	Mild	29.8	41.1	37.9	22.1	31.2	41.1

*Calculated in Percent of Predicted Normal.

chronic asthma. In twenty-eight of these patients, relief was obtained within three to five minutes, and this relief increased up to a maximum within fifteen minutes or less. The relief was comparable to that obtainable, under similar circumstances, from 0.3 to 0.5 mg of epinephrine, but without the side effects of tremor, tachycardia, nervousness, et cetera. There are occasions when a severe chronic patient, in a paroxysm, obtains very little relief from an epinephrine injection. Similarly, in two of our cases, although relief was obtained, it was minimal. Two patients failed to respond. Figure 1 illustrates the changes in vital capacity and maximal breathing capacity which were observed in a few of these patients. It is obvious that the improvement after the new agent was great (the results of the tests are calculated in terms of the per cent of the expected normal.)

Group 2.—The fifteen chronic asthmatic patients in this group were tested spirometrically before and fifteen minutes after injections of 25 mg of Prantal, subcutaneously. All patients were in a state free of asthmatic dyspnea. Table I details the changes which took place in the vital capacity and maximal breathing capacity of these patients.

This drug was tested twenty-six times in all. Injected subcutaneously, it caused an increase in the vital capacity in nineteen out of twenty-six trials during a nondyspneic phase. The increase was over 15 per cent in twelve of these trials, or 46.1 per cent of the trials. Similarly, injections of the drug effected an increase in maximal breathing capacity in nineteen out

of twenty-six trials, again twelve showing a rise of 15 per cent or more. Although seven trials showed a rise in both vital capacity and maximal breathing capacity of 15 per cent or more, in only two trials was there any correspondence between the rise in the two tests.

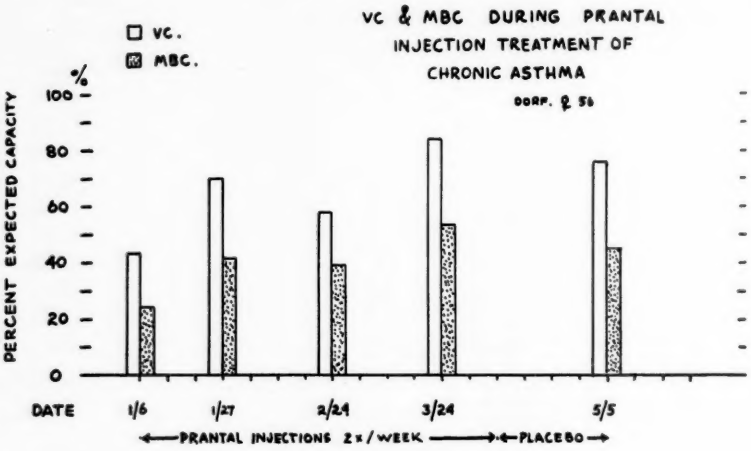

Fig. 2(a)

Two things are obvious from the Table I. Changes in maximal breathing capacity after the drug do not necessarily parallel changes in vital capacity. In addition, in the resting stage between dyspneic attacks, one cannot predict, from the severity of the chronic asthma, which case is apt to show an increase, or to what degree, in vital capacity and maximal breathing capacity.

Group 3.—Since several patients on Prantal injections had remained free of asthma for several days, eleven patients were started on the injections of 25 mg, subcutaneously, twice weekly. At the end of the first week of treatment, three patients refused further injections and at the end of the second week two more stopped treatment. One developed chest pains (this patient was also on nitroglycerine), one was much worse, and three remained essentially the same, with distressing side effects. This ill effect occurred within a few hours after the injection and was described as due to the marked increased drying effect on their secretions, with consequent difficulty in raising sputum. The other six patients were continued on injections for three months, after which they were given saline injections instead. Of this group, one had mild asthma with chronic otorrhea, another mild asthma with chronic myocarditis, three had moderately severe asthma, and one had a very severe asthma with marked emphysema and cor pulmonale. Histories taken on all patients included notations on the average amounts and kinds of medications they were using for

symptomatic relief, and on the average amount of asthmatic symptoms which occurred daily. Patients were given charts each week for the daily recording of their symptoms and medications used. It became our studied opinion that a patient should not be considered to have achieved a fair

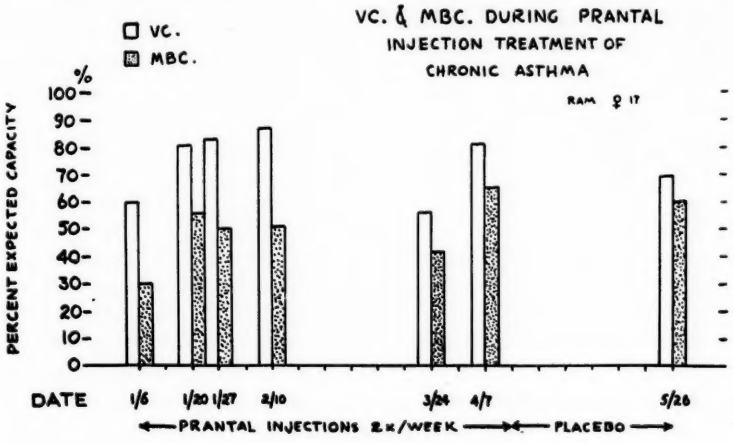

Fig. 2(b)

result unless his day to day record showed a 50 per cent or more improvement. In evaluating the symptoms and medications on the patients' daily record, we felt the method adopted by Lowell and Schiller[6] was too arbitrary for our purposes. Our patients recorded their symptoms numerically. We decided to give cough a value of one, wheeze a value of two, and dyspnea a value of three. We assigned to potassium iodide, cough mixtures, asthma powders, and cigarettes a value of one; aminophyllin tablets and suppositories a value of two; ephedrine products, Isuprel® and epinephrine or Isuprel nebulizers a value of three; and epinephrine and aminophyllin injections a value of four. Symptoms were summed up for the week as a group, as were drugs, these were added to each other, and equilibrated by dividing by two. This was compared to the standard set up for each patient for drugs and symptoms (before the drug was started) to obtain the degree of improvement or lack of it. (This same set up for each patient for drugs and symptoms (before the drug was contrasted to the objective spirometric changes in vital capacity and maximal breathing capacity obtained after treatment.

Four of the six patients treated with Prantal injections for three months showed a 50 per cent or more clinical improvement. These same patients did as well, or better on saline injections. Two patients showed only slight clinical improvement on injections of the drug and were worse on saline injections. Figure 2(a) illustrates the changes in vital capacity and maximal breathing capacity on drug and on saline injections obtained

TABLE II. CLINICAL STATUS AND SPIROMETRIC FINDINGS IN CHRONIC ASTHMATICS TREATED WITH PRANTAL INJECTIONS

Patient	Severity of Asthma	Type of Injection	Percentage of Improvement Over the Untreated State		
			Clinical Status	Vital Capacity	Maximal Breathing Capacity
1. Dorf	Mild with Otorrhea	Prantal	94.	100.	81.
		Saline	100.	74.	52.
2. Rich	Mild with Myocarditis	Prantal	60.	19.	− 9.
		Saline	60.	12.	−18.
3. Wash	Mod.	Prantal	68.	28.	36.
		Saline	68.	− 2.	33.
4. Baxt	Very Severe with Emhysema	Prantal	31.3	4.	− 0.3
		Saline	21.	−16.	−20.
5. Ram	Mod.	Prantal	49.	42.	101.
	Severe	Saline	67.	37.	112.
6. Roo	Mod.	Prantal	12.6	−15.4	−13.
		Saline	4.	−32.3	−39.

in one mild case and Figure 2(b) in one moderately severe asthmatic patient. Table II gives the clinical and spirometric results in more detail.

After reviewing our tests on nondyspneic asthmatic patients, it would be in our opinion conservative judgment to state that 15 per cent improvement in one of these tests was significant. Roy et al[11] found an increase of 14.1 per cent after administration of epinephrine in active asthma. It will be noted that in the four improved cases in this group, this figure was attained in all the tests save one (maximal breathing capacity in Case 2.) In every instance, save one (maximal breathing capacity Case 4), the vital capacity and maximal breathing capacity became worse when the patient was placed on saline injections, despite the fact four of the cases maintained the same or showed better clinical improvement on the saline injections. Since the improved clinical state on saline injections persisted for two months, we are inclined to feel this may either be due to a prolonged remission induced by the Prantal, or that a psychologic factor has substituted for the benefits from the drug.

Group 4.—Twenty-two cases were started on enteric coated Prantal tablets, 200 mg four times daily. Four of these patients stopped after one week because of failure to improve and were placed on injection therapy. One patient was excluded from our tabulations because of inadequate cooperation. The other seventeen took the tablets in the doses mentioned for from two weeks (three cases) to fifteeen weeks, at which time they were given indentically appearing especially prepared placebo tablets. In this group, again daily reports of symptoms and the medications taken were recorded, and again clinical charts were given graded values. Ten of the remaining seventeen patients stated definitely they felt appreciably better on Prantal tablets, orally. Because the results, as presented in Table III, represent averages over all the weeks of treatment, and since one or two bad weeks might easily bring down an average, only three patients showed an improvement of over 50 per cent; these were 52, 56 and 60 per cent. Six other patients, however, were close to a fair

TABLE III. RESULTS IN CHRONIC ASTHMATICS TREATED WITH PRANTAL TABLETS AND PLACEBO

Patient		Percentage		Percentage of Predicted Normal					
		Clinical Improvement During Treatment		Vital Capacity			Maximal Breathing Capacity		
		Range	Average	Before Treatment	After Treatment	Gain	Before Treatment	After Treatment	Gain
1. AMA	Prantal	−35.5 to 94.5 69.	60.	90.4	89.0	—	76.6	74.6	—
	Placebo	85. to 35.	77.	89.0	91.6	2.9	74.6	64.7	—
2. BRL	Prantal	73.	56.	26.6	36.4	36.8	18.9	23.6	29.0
	Placebo	43. to 62.	51.	36.4	28.7	—	23.6	18.9	—
3. FERR	Prantal	−69. to 73.0	40.	52.7	47.5	—	67.9	68.5	0.8
	Placebo	23. to 73.	59.	47.5	47.2	—	68.5	62.5	—
4. GOM	Prantal	26. to 68.	49.	75.0	73.0	—	101.0	80.5	—
	Placebo	34. to 45.	40.	73.0	68.5	—	80.5	76.5	—
5. GON	Prantal	41. to 50.	45.	63.0	59.0	—	37.2	55.0	47.9
	Placebo	25. to 64.	44.	59.0	72.3	22.5	55.0	53.0	—
6. GUER	Prantal	−45. to 65.	7.	58.3	55.1	—	78.0	70.0	—
	Placebo	−28. to 24.	1.	55.1	61.0	10.7	70.0	75.0	7.1
7. LAK	Prantal	−79. to 67.	21.	73.9	68.2	—	30.6	50.8	65.6
	Placebo	−13. to 53.	15.	68.2	47.6	—	50.8	39.4	—
8. NEW	Prantal	−42. to 28.	−19.	48.3	45.2	—	31.1	22.1	—
	Placebo	−89. to −3.	−44.	45.2	31.8	—	22.1	17.7	—
9. TURN	Prantal	33. to 67.	45.	35.4	26.3	—	25.4	12.8	—
	Placebo	40. to 60.	52.	26.3	32.8	24.7	12.8	20.3	58.6
10. BAN	Prantal	12. to 74.	47.	67.	63.	—	33.	36.	9.9
11. DAV	Prantal	6. to 57.	35.	19.	29.	50.2	19.0	21.7	14.2
12. HOP	Prantal	−13. to 94.	47.	35.	42.4	21.1	34.6	34.6	—
13. LEW	Prantal	12. to 48.	32.	62.	51.	—	35.	36.	2.8
14. RUI	Prantal	−35. to 78.	37.	Inadequate Testing					
15. JAC	Prantal	0. to 0.	0.	Short Treatment—No follow-up tests					
16. KID	Prantal	18. to 21.	19.5	Short Treatment—No follow-up tests					
17. LEO	Prantal	47. to 58.	52.5	Short Treatment—No follow-up tests					

result with 40, 45, 45, 47, 47 and 49 per cent, respectively. Nine of the seventeen patients were placed on placebo tablets after five to fifteen weeks of treatment.

Table III shows that of thirteen estimations, on thirteen cases, of both vital capacity or maximal breathing capacity before and after oral therapy with the anticholinergic agent, there were only three instances (23 per cent) in which the improvement in vital capacity was over 15 per cent, compared to eight cases (61.5 per cent) of this same group who improved 40 per cent or more, clinically. Two of nine in this group treated with placebo tablets (32 per cent) also showed greater than 15 per cent increase in vital capacity. In only three instances (23 per cent) was the maximal breathing capacity improved 15 per cent or more. One (12 per cent) of the placebo cases showed 15 per cent or more increase in maximal breathing capacity. Again, of seventeen cases on Prantal tablets, nine (52.9 per cent) showed statistically 40 per cent or more clinical improvement. Six out of nine (66.6 per cent) of the placebo cases did this well also (although an equal number were slightly worse on placebo than on tablets containing the drug). In neither group were the variations great enough to lend extra weight to the value of the tablets, therapeutically. The maintenance of relatively the same results with placebo tablets could best be interpreted as due to either psychologic factors or a carry over of the beneficial results obtained while on the drug.

A word should be said about side reactions encountered with Prantal.

There occurred, as expected, from the known pharmacology of the drug, such reactions as drying of mucous membranes, blurred vision, stuffy nose, and abdominal cramps. Also noted were headache, nausea, vomiting, dysuria, chest pains, leg pains and nervousness. Only the drying was of consequence to the asthmatic state. The other reactions were neither too severe or distressing.

DISCUSSION

In evaluating any drug one must consider its theoretical, pharmacologic and clinical aspects. The inhibition of parasympathetic impulses to the bronchial musculature is theoretically sound. Pharmacologically, Prantal and other anticholinergic drugs produce such inhibition. Clinically, patients in an acute asthmatic state, as found in our Group I, derived definite help from this action. This product has proved its usefulness in the acute paroxysmal asthmatic state.

On the other hand, inhibition of parasympathetic impulses to the bronchial mucosal cells results in a drying up of bronchial secretions. In many patients with chronic asthma who have thick obstructive secretions or plugs, this action presents a distinct clinical disadvantage. The patients placed on the new drug, both orally and by injection, who stopped therapy early because of difficulties they encountered due to drying effects, are an example of this. Drying effects were felt in many who remained on therapy, but to a tolerable degree. With this drawback in mind, one must raise speculatively the question whether this product given in aerosolized form, or by injection in a slowly absorbed form, might not be better for the treatment of chronic cases. Theoretically, it may be possible to develop a mixture of drugs with great blocking action on the parasympathetic fibres to the bronchial musculature and very little on the mucosa. Until such a mixture of drugs is developed, the answer to this dilemma may be the combined use of an anticholinergic, like Prantal, and a mucolytic agent which liquefies bronchial secretions. Our investigation of Prantal is simply an exploration of another pharmacologic approach to the problem of asthma.

SUMMARY

1. Of thirty patients in an acute asthmatic paroxysm, twenty-eight were substantially relieved within a few minutes by an injection of Prantal, in adequate dosage, subcutaneously.

2. Of fifteen chronic asthmatic patients, in a nondyspneic phase, who were tested twenty-six times before and after the drug was injected subcutaneously, an increase in vital capacity of 15 per cent or more was shown in twelve trials, in nine cases after Prantal. A similar increase of 15 per cent or more in maximal breathing capacity was shown in twelve of twenty-six trials in eight patients after use of the drug. These results suggest that this anticholinergic drug is an active bronchodilating agent in asthma.

3. Of six chronic asthmatic patients treated over a long period of time with injections of this drug twice weekly, four appeared benefited and showed at least a 20 per cent increase in respiratory function when tested for vital capacity and maximal breathing capacity. All tests except one showed decreased function when the six patients were placed on saline. Four patients demonstrated a fair clinical improvement on the saline injections.

4. Of seventeen patients placed on tablets containing the drug, 200 mg four times daily, nine showed subjective improvement of 40 per cent or more. Only three cases showed 15 per cent or better improvement in vital capacity or maximal breathing capacity. Three of nine patients were better on placebo tablets than on the drug.

5. The data are insufficient to attribute substantial therapeutic benefits to Prantal taken on a long term basis, orally, or by intermittent injections.

6. Five patients had to discontinue injections of the drug quickly, and four discontinued the tablets because of the excessive drying effect.

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7949 Vineland St. (Dr. Frank)

THERAPEUTIC EFFECTIVENESS OF ELIXOPHYLLIN FOR THE ORAL TREATMENT OF ACUTE AND CHRONIC BRONCHIAL ASTHMA

AARON D. SPIELMAN, M.D., F.A.C.A.
New York, New York

DURING an accute asthmatic attack, there is a marked decrease in the vital capacity and the inspiratory, and particularly, the expiratory air velocity rates. These changes are in large part secondary to the severe bronchospasm which occurs during a paroxysm of asthma. The xanthine group of drugs, by relieving bronchospasm[1] and consequently increasing the vital capacity and maximum breathing capacity, favor a return to normal of the oxygen tension and blood oxygen saturation. Of the xanthine group, theophylline has the most potent bronchodilating action. The clinical improvement, both subjective and objective, often seen following the administration of theophylline and the subsequent increase in vital capacity, attests to its effectiveness in relieving bronchiolar smooth muscle spasm.[1,2]

Intravenous aminophylline (theophylline ethylenediamine) has been used for many years to terminate acute asthmatic attacks. Although well established and effective, this route of administration has the disadvantage of having to be administered by a physician. Occasionally this route causes severe side reactions and even sudden death. The prompt response following intravenously administered aminophylline, in contrast to the relative ineffectiveness of orally administered aminophylline in a similar situation, apparently indicates that, to a large extent, the relief obtained from aminophylline is dependent upon the height of the blood theophylline level, and the rapidity with which it is attained.[2-4]

In their studies on blood theophylline levels after the administration of aminophylline by various routes, Waxler and Schack[5] observed that the intravenous injection of 0.25 gm of aminophylline produced a mean value of 6.0 micrograms of theophylline per ml of blood, one-half hour following the injection. After the oral administration of 0.2 gm of aminophylline in an uncoated tablet, the mean blood theophylline level one-half hour after administration was 1.5 micrograms per ml of blood; one-half hour after 0.5 gm of aminophylline was introduced by rectal suppository, the mean blood theophylline level was only 0.5 micrograms per ml of blood.

As shown by Waxler and Schack,[5] the absorption of aminophylline following administration by rectal suppository is erratic and undependable. Some subjects had no appreciable blood theophylline levels until the fifth and sixth hours, while others had very high levels after four

*Elixophyllin—Sherman Laboratories, Detroit, Michigan. The author wishes to thank Dr. Frank P. Panzarella for his help in planning this study.

hours. Unpredictable absorption coupled with repeated administration can lead to dangerous cumulative effects with serious toxicity particularly in infants and young children. Nolke[6] reported thirteen cases of severe toxic effects following the use of aminophylline and theophylline suppositories in children, resulting in four deaths. Four cases of poisoning following administration of aminophylline suppositories are reported by Rounds[7] and an additional four cases by Love and Corrado.[8]

Although the oral administration of aminophylline tablets produces inadequate blood theophylline levels for the alleviation of an acute attack of asthma, the repeated oral administration of aminophylline in doses of 0.2 gm to 0.4 gm is efficacious in chronic asthma. With the use of the higher doses however, unpleasant gastrointestinal side effects are frequently encountered.

The present study was undertaken to evaluate the efficacy of Elixophyllin for the treatment of acute and chronic asthma. Elixophyllin is a hydro-alcoholic solution containing 80 mg of free theophylline and 3 ml of ethyl alcohol per tablespoonful (15 ml). Each tablespoonful contains the theophylline equivalent of 100 mg of aminophylline. Since the theophylline present in Elixophyllin is in the free form, more rapid and efficient absorption occurs than from tablets of theophylline salts. Unlike aminophylline and similar basic salts of theophylline, the theophylline present in this hydro-alcoholic solution is not precipitated onto the gastrointestinal mucosa by the action of hydrochloric acid. Thus the direct irritant effect of theophylline on the gastrointestinal tract is greatly minimized.

The alcohol present in Elixophyllin also aids in the rapid absorption of the free theophylline present in the solution. It should be noted, however, that Brown[9] has successfully employed a solution of five per cent alcohol in glucose and saline intravenously in the treatment of status asthmaticus. Thus additional therapeutic benefit may be expected from the alcohol content of Elixophyllin.

Schluger, McGinn and Hennessy[10] reported mean blood theophylline levels of 8.0 micrograms and 10.3 micrograms per ml of blood fifteen and thirty minutes, respectively, following the oral administration of a single dose of 5 tbsps (75 ml) of Elixophyllin. When the same subjects were given the theophylline equivalent dose in the form of 0.5 gm of uncoated aminophylline tablets, the blood theophylline levels after fifteen and thirty minutes were only 1.1 micrograms and 3.8 micrograms per ml of blood, respectively.

Oscharoff[11] determined the blood theophylline levels obtained after repeated oral administration of Elixophyllin compared with repeated oral administration of the equivalent dosage of aminophylline. He showed that the mean blood theophylline levels were maintained at a significantly higher level following the administration of Elixophyllin.

TABLE I. PATIENT DATA

Group	No. of Patients	Age in Years	Sex		Type of Asthma		Duration of the Disease in Years
			Male	Female	Infectious	Mixed	
A: Severe acute asthmatic attack	20	9 over 50 7, 30 to 50 4, under 30	14	6	15	5	5 less than 5 years 15 more than 5 years
B: Mild chronic asthma	11	9 over 40 2 under 30	2	9	3	8	4 more than 5 years 7 less than 5 years
Moderately severe chronic asthma	11	5 over 40 6 under 30	5	6	6	5	6 more than 5 years 5 less than 5 years
Severe chronic asthma	8	6 over 50 1, age 34 1, age 12	3	5	6	2	all less than 5 years
Totals	50		24	26	30	20	

SELECTION OF PATIENTS

Fifty patients with asthma of the infectious and mixed types were selected for the purposes of this study. They comprised forty-five adults and five children, the youngest of whom was six years old (Table I). The patients were divided into two groups: Group A, composed of twenty patients who were seen during a severe acute asthmatic attack, and Group B, composed of thirty patients with chronic asthma and constant wheezing. Eleven patients had mild asthma; eleven had moderately severe asthma; eight had severe asthma.

METHOD OF EVALUATION

To evaluate the efficacy of a single large oral dose of Elixophyllin in the treatment of a severe acute asthmatic attack, the twenty patients who presented themselves for treatment during an acute asthmatic paroxysm were given a single dose of 5 tbsps (75 ml) of Elixophyllin. Prior to the administration of the medication, vital capacity measurements were performed. These measurements were repeated five, fifteen and thirty minutes following the administration of Elixophyllin. Results were judged on the basis of subjective and objective clinical improvement together with changes in the vital capacity.

The evaluation of Elixophyllin in the treatment of chronic asthma was based on the study of the thirty patients in Group B. Treatment of this group of patients was begun in October, 1955, after the ragweed pollen season was over, and the study was continued for six months through the winter of 1955-56. Eleven patients with mild asthma were given 0.2 gm of aminophylline three times a day for one month and at the end of this time changed to Elixophyllin 2 tbsps three times daily. Eleven patients with moderately severe asthma were given 0.2 gm of aminophylline four times daily for one month and then changed over to Elixophylline 2 tbsps on the same schedule. The eight patients with severe chronic asthma were divided into two subgroups of four patients each. One subgroup of four patients was given 0.3 gm of aminophylline and the other subgroup 0.4 gm of aminophylline three times a day for one month. At the end of

TABLE II. INDIVIDUAL RESULTS OF TREATMENT OF SEVERE ACUTE ASTHMATIC ATTACK WITH SINGLE ORAL DOSE OF 5 TBSPS. (75 ML) OF ELIXOPHYLLIN

Case	Sex	Age	Type of Asthma	Duration of Disease in Years	Clinical Response	Vital Capacity			
						Before ℞	After ℞		
						cc	5 Min. cc	15 Min. cc	30 Min. cc
1	M	38	Infectious	5	Excellent	2400	2700	2800	3200
2	M	58	Infectious	3	Excellent	1700	2100	2200	2400
3	M	35	Mixed	10	Excellent	2200	2700	3000	3400
4	M	55	Infectious	12	Good	1500	1700	2000	2100
5	F	37	Infectious	3½	Excellent	2400	2800	2900	3200
6	M	22	Infectious	11	Excellent	2250	2500	2700	3000
7	M	18	Infectious	5	Good	1900	2050	2300	2450
8	M	45	Infectious	2	Excellent	2100	2500	2800	3200
9	M	56	Infectious	7	Good	1700	1850	2100	2200
10	F	51	Infectious	5	Good	2300	2550	2700	2850
11	M	49	Mixed	10	Excellent	1950	2400	2800	3000
12	M	29	Mixed	15	Excellent	2400	2700	2950	3300
13	M	54	Infectious	20	Excellent	1700	2000	2400	2650
14	M	24	Mixed	5	Excellent	2300	2500	2800	3200
15	F	54	Infectious	3	Excellent	1800	2100	2500	2700
16	M	59	Infectious	7	Good	2500	2600	2900	3150
17	F	63	Mixed	23	Excellent	2350	2800	3000	3250
18	M	62	Infectious	15	Excellent	2100	2650	3000	3050
19	F	36	Infectious	5	Good	1800	1950	2200	2300
20	F	42	Infectious	3	Excellent	2400	2600	3000	3300

TABLE II-A. SUMMARY OF RESULTS OF TREATMENT OF SEVERE ACUTE ASTHMATIC ATTACK WITH SINGLE ORAL DOSE OF 5 TBSPS. (75 ML) OF ELIXOPHYLLIN

Patients No.	Type of Asthma		Clinical Response	Average Vital Capacity			
				Before ℞	Average Increase After ℞		
	Infectious No.	Mixed No.		cc	5 Min. cc	15 Min. cc	30 Min. cc
14	9	5	Excellent	2143	2503 (17%)	2775 (29%)	3060 (43%)
6	6	0	Good	1950	2117 (9%)	2366 (21%)	2508 (29%)

this period, both subgroups were given 3 tbsps of Elixophylline three times daily. (After one week, the dosage schedule was reduced by half in the four children with mild and moderately severe asthma and reduced by a third in the child with severe asthma.) In all patients, following a month of continuous Elixophyllin administration, the medication was continued on a p.r.n. basis.

In evaluating the results of treatment, the three cardinal symptoms of asthma were considered, i.e. cough, wheezing and dyspnea. Those patients showing 75 per cent or more improvement were considered as having excellent results; those showing 50 to 75 per cent improvement were considered showing good results; those patients showing 50 per cent or less improvement were considered to have equivocal results.

RESULTS

Group A:—The twenty patients in this group were seen and treated during a severe acute asthmatic attack. Vital capacity measurements were taken prior to the administration of a single dose of 5 tbsps of Elixophyllin

TABLE III. SUMMARY OF RESULTS OF TREATMENT WITH REPEATED DOSES OF ELIXOPHYLLIN AND AMINOPHYLLINE

Severity of Asthma	Drug and Dose	Length of Treatment, Months	Patients, No.	Clinical Response			Side Effects
				Excellent, No.	Good, No.	Equivocal, No.	
Mild	Aminophylline 0.2 gm. t.i.d.*	1	11	1	9	1	1 patient complained of slight nausea
	Elixophyllin 2 tbsps. t.i.d.*	1	11	8	2	1	Same patient complained of slight nausea
	Elixophyllin p.r.n.	1 to 4	10	8	1	1	None
Moderately severe	Aminophylline 0.2 gm. q.i.d.**	1	11	0	9	2	None
	Elixophyllin 2 tbsps. q.i.d.**	1	11	8	1	2	None
	Elixophyllin p.r.n.	1 to 4	11	8	1	2	None
Severe	Aminophylline 0.3 gm. t.i.d.***	1	4	0	2	2	None
	Elixophyllin 3 tbsps. t.i.d.***	1	4	4	0	0	None
	Elixophyllin p.r.n.	1 to 4	4	4	0	0	None
Severe	Aminophylline 0.4 gm. t.i.d.	1	4	4	0	0	2 patients complained of marked gastrointestinal upset
	Elixophyllin 3 tbsps. t.i.d.	1	4	4	0	0	None
	Elixophyllin p.r.n.	1 to 3	4	4	0	0	None

*Daily dose reduced by one-half after the first week in child of 10 years of age.
**Daily dose reduced by one-half after the first week in 3 children of 6, 9, 10 years of age.
***Drugs were taken 3 times a day for first week and reduced by ⅓ for remainder of month in child of 12 years of age.

and at five, fifteen and thirty minutes following administration. All twenty patients initially showed a marked reduction in the vital capacity (Table II). There was clinical evidence of marked bronchospasm on auscultation of the lungs. Following administration of Elixophyllin, there was a gradual increase in the vital capacity in all cases beginning at five minutes, with further increases noted at fifteen and thirty minutes. The average increase in vital capacity after thirty minutes was 740 ml (Table IIA. The increase in vital capacity was paralleled by clinical improvement. There was marked clearing of the previously heard asthmatic wheezing and the prolonged expiration was measurably lessened. Fourteen patients were classified as having had excellent results while six patients had good results.

Group B (Table III):—In the patients with mild and moderately severe asthma, fifteen of twenty-two patients experienced greater relief while taking Elixophyllin than while taking the theophylline equivalent dose of aminophylline tablets. In the remaining seven patients the results were the same with both medications.

In the subgroup of four patients with severe asthma treated with 0.3 gm of aminophylline three times daily, greater improvement was noted when the theophylline equivalent dose of 3 tbsps of Elixophyllin three times a day was substituted for the aminophylline.

In the subgroup of four patients with severe asthma who were initially

given three daily doses of 0.4 gm aminophylline and then changed to 3 tbsps of Elixophyllin on the same schedule, the results of treatment with Elixophyllin were as good as with aminophylline despite the fact that this represented a lower theophylline equivalent dose than the 0.4 gm of aminophylline. Two of the four patients had severe gastrointestinal upsets while taking the prescribed dose of aminophylline, but none of the patients experienced gastrointestinal difficulties while taking Elixophyllin.

DISCUSSION

The results obtained in the twenty patients treated with Elixophyllin during an acute asthmatic attack clearly indicate that this oral medication is a rapid, effective and safe means of terminating an acute asthmatic paroxysm. The subjective criteria for improvement were supported by the measured increases in vital capacity in all cases. That the single large dose employed is capable of inducing rapid high blood theophylline levels has been demonstrated.[10] It has been shown that much higher blood theophylline levels are obtained fifteen and thirty minutes following the oral administration of 75 ml of Elixophyllin[10] than those reported following 0.25 gm of aminophylline intravenously and 0.5 gm of aminophylline intramuscularly.[5]

A theophylline preparation which can be administered orally and yet give the same results as intravenously administered aminophylline has much to recommend it. Patients prone to sudden acute attacks of asthma can be instructed to take Elixophyllin at home, thus avoiding the necessity for emergency visits by the physician or visits to a hospital emergency room by the patient. The intravenous administration can be eliminated in the majority of patients and the dangers incident thereto avoided.

In the group of patients with chronic asthma, Elixophyllin was more effective in relieving symptoms in nineteen of twenty-six patients than the theophylline equivalent dose of aminophylline. In the remaining seven patients both drugs were equally effective. An additional four patients obtained an equal degree of relief from a dose of Elixophyllin which contained less theophylline than the previously administered aminophylline. The greater effectiveness of Elixophyllin would appear to be related to the sustained higher theophylline blood levels reported.[11]

The alcohol present in Elixophyllin, in addition to aiding in the rapid absorption of the theophylline, in itself may provide additional therapeutic benefit as suggested by Brown.[9] The distressing gastrointestinal effects seen when high doses of aminophylline are given do not occur with high doses of Elixophyllin.

SUMMARY

1. A single oral dose of 5 tbsps (75 ml) of Elixophyllin is effective in terminating severe acute asthmatic attacks.

2. Repeated doses of Elixophyllin proved more effective than com-

parable doses of aminophylline in mild, moderately severe and severe chronic asthma with persistent wheezing.

3. The therapeutic effectiveness of Elixophyllin is chiefly ascribed to the faster and more efficient absorption of theophylline from the gastrointestinal tract.

4. Elixophyllin, being singularly free of any side effects in children as well as adults, can be used daily in chronic asthma for the steady maintenance of therapeutic blood theophylline levels. This procedure will give the best results.

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141 E. 56th Street

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ANNALS SUBSCRIPTIONS AND NONPAYMENT OF DUES

At its meeting held in November, 1956, the Finance Committee of The American College of Allergists recommended that the following notice be printed in the May-June, 1957, issue of the ANNALS OF ALLERGY:

"During a discussion which followed a statement of Dr. Mitchell, it was pointed out that most of the members who had not paid their dues continued to receive the ANNALS, and should be notified that if they wished their subscriptions to continue their dues should be paid. It was suggested that a notice be sent out with the bills stating that the subscription to the ANNALS would be discontinued until dues were paid. It was suggested that a notice be put in the ANNALS OF ALLERGY, reading as follows:

"NOTICE"

"By order of the Board of Directors, all members more than six months in arrears in the payment of their College dues will no longer receive the ANNALS from and after this issue."

THE CLINICAL IMPORTANCE OF FOOD DISLIKES IN ALLERGIC CHILDREN

MARY S. BOYDEN, M.D.
Lawrence, Kansas
and
JEROME GLASER, M.D., F.A.C.A.
Rochester, New York

THE PROBLEM of food dislikes is very complicated and involves many psychologic factors including the associations which arise in conjunction with the taste, odor, color and consistency of any particular food, the attractiveness of its preparation and customs regarding food in the environment in which the individual lives. If father refuses to eat peas, it is very likely that son Johnny won't like peas either.

In the case of those suffering from allergic diseases, it has often been stated that dislike of a food is frequently a defensive reaction against a harmful food. Williams[1] in 1936 studied a group of 150 out of 18,500 elementary school children in Cardiff, Wales, who refused milk at school and found that eighty-eight (58.7 per cent) refused because ingestion was always followed by an allergic manifestation of some sort (nausea or vomiting in all but four) and that an additional 24 per cent had no symptoms but had a personal or family history of allergy. However, in a series of 500 individuals including fifty-seven with frank major allergies and 249 with a past history of minor allergic symptoms, Vaughan and Pipes[2] found that in only about 20 per cent of the combined group of allergic patients expressing food dislikes was there any correlation between dislike of even one food and allergic symptoms, and that of all the disliked foods only 4.8 per cent were recognized by the patient as provocative of allergic symptoms. In a group of nineteen patients in whom skin tests were checked against food dislikes, only 12.7 per cent of disliked foods gave positive or borderline tests. They therefore concluded that, except when gastrointestinal symptoms follow ingestion promptly, food dislikes cannot be relied on as an index of allergy. In discussing their paper, Rappaport suggested that a careful history of food likes and dislikes in children under the age of three or four years might give a different picture.

In an attempt to determine whether there is a higher correlation between food dislikes and allergic reactions in a younger age group, we made a study of the records of 560 children twelve years of age or younger in the private practice of one of us (JG). These children all had one

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From the Department of Pediatrics of the University of Rochester School of Medicine and Dentistry and the Pediatric Services of the Genesee Hospital and the Strong Memorial-Rochester Municipal Hospitals, Rochester, New York.
Dr. Boyden is a Fellow in Pediatric Allergy.

TABLE I. 560 CHILDREN WITH MAJOR ALLERGIES

Age	No.	With Food Dislikes	Without Food Dislikes
0-4 years	200	99	101
4-12 years	360	218	142
Total	560	317 (57%)	243

TABLE II. FOOD DISLIKES OF 560 ALLERGIC CHILDREN

Foods	Under Age 4 (200)	4-12 Years (360)
No foods	101 (50%)	142 (39%)
Vegetables	49 (24%)	122 (34%)
Egg	16 (8%)	48 (13%)
Meat	11 (5%)	30 (8%)
Milk	12 (6%)	18 (5%)
Fish	2	13
Fruit	7	9
Chocolate	2	3

Cereal, bread, creamed foods, sweets, spaghetti, nuts, peanut butter, soup, desserts, cheese, ice cream, pudding, etc. listed occasionally.

or more of the following: perennial asthma, perennial allergic rhinitis, chronic atopic dermatitis or recurrent upper respiratory infections considered to be on an allergic basis. The records were taken consecutively from the file and were unselected except that only those cases which had been thoroughly and satisfactorily studied were included. In the course of the routine work-up, a history was taken of food likes and dislikes as well as food disagreements, and complete testing for foods was done. The skin tests for foods were confined to scratch tests except that intradermal tests were also done for egg white and fish. Food tests were not considered positive unless confirmed by recheck. When divided into two groups above and below the age of six years, no significant differences were found between the younger and older groups in the first 500 children studied. Therefore, because of Dr. Rappaport's suggestion, the children were divided into two additional groups, one below the age of four and the second between ages four and twelve. In order to increase the number of children in the younger group to 200, sixty more children in that age group, taken consecutively from the files, were added, making the total number of children in the study 560.

Table I shows the distribution of the children in the two groups and the number in each group with food dislikes. Approximately half of the younger children and 60 per cent of the older children indicated one or more food dislikes on routine questioning. This is somewhat lower than the 80 per cent found by Vaughan and Pipes[2] in their study. As can be seen from Table II, the most commonly disliked foods in both groups were vegetables, either named individually or in the aggregate, with egg second and meat third. Of the meats, liver was the most frequently named. In many instances, rather than individual foods, classes of foods such as vegetables or cereals were mentioned; in others, modes of prepa-

TABLE III. FOODS CAUSING SYMPTOMS

Group I—104 Disliked Foods				Group II—239 Disliked Foods			
Age	Food	ST	Symptoms from History	Age	Food	ST	Symptoms from History
1½	potato	−	gagging	4	egg	−	rash
8m	milk	−	*eczema	4½	egg	−	vomiting
2	egg	+	vomiting	4½	egg	−	gagging
20m	egg	+	vomiting, urticaria	4½	egg	−	"funny feeling in throat"
2½	egg	+	*asthma	5	peas	−	gagging
	milk	−	*asthma	5½	egg	+	asthma, rash
2½	egg	+	*asthma	5½	egg	−	asthma
3½	egg	+	eczema	5½	egg	−	gagging
8m	spinach	+	0	6½	peas	−	vomiting, fever
12m	pea	+	0	7	egg	−	burning of tongue and circumoral redness
14m	spinach	+	0		spinach	+	
20m	peanut	+	0		beets	−	
3	spinach	+	0		orange	−	
3	spinach	+	0	8	egg	−	cough
	gr. bean	+	0	9	egg	−	asthma
				10½	tomato	+	rash
				10½	egg	−	eczema
				10½	egg	−	vomiting, asthma
				11	egg	−	nausea
				4	spinach	+	0
				6	potato	+	0
				7	peanut	+	0
				7½	spinach	+	0

ST = skin test.
m = age in months; otherwise age is indicated in years.
* = improved on elimination of suspected food.

TABLE IV. MILK DISLIKE IN 560 CHILDREN

	0-4 Years	4-12 Years	Total
Number	12	18	30
Symptoms	1?	0	1?
Improved	2	0	2
When Eliminated	1?		1?
Not Improved			
When Eliminated		5	5
No Report		3	3
Not Eliminated	8	10	18

ration such as "cooked carrots" or "tomato soup" were described. However, there were 343 individual foods mentioned by 219 of the children.

Table III shows the foods causing symptoms or giving positive skin tests out of the 104 individual foods disliked by the younger group and the 239 disliked by the older group. There was correspondence between food dislike and clinical symptoms in only 8 per cent of foods in both groups, with an additional 6 per cent in the younger group and 2 per cent in the older group giving positive skin tests without clinical symptoms. Five out of the eight foods causing symptoms in the younger group, and thirteen out of the nineteen in the older group, were egg. When the incidence of clinical symptoms in the group of sixty-four children disliking egg was compared with that in the 253 children who had food dislikes but did not dislike egg, it was found that eighteen (28 per cent) of those disliking egg had clinical symptoms, while only twenty-eight (11 per cent) of those not disliking egg had symptoms. However, there were an additional twenty-six (10 per cent) in the latter group with positive skin tests and no symptoms (nine were in the younger group and had not had egg) and if these are included, there is little difference between the groups. In almost half (eight out of eighteen) of the group

disliking egg the symptoms were gastrointestinal, while in less than one-fourth (six of twenty-eight) of the group not disliking eggs were the symptoms gastrointestinal.

Table IV summarizes our findings with regard to milk dislike among these children. Of thirty children disliking milk, one had questionable symptoms from milk, two were improved when milk was eliminated, and one was questionably improved. Most of the remainder were either unimproved by the elimination of milk or responded so satisfactorily t other measures that milk was not eliminated from the diet. While the numbers are too small to draw any definite conclusions, there does no appear to be any close correlation between dislike of milk and allergic reactions to milk.

Therefore, from this study of 560 children with major allergies, the conclusion must be drawn that even under the age of four years, the correlation between food dislikes and allergic reaction to disliked food is low; that food dislikes are not helpful as an index of allergy except possibly in the case of egg, and that even in the case of egg, the higher correspondence between dislike and disagreement probably results from the higher incidence of prompt gastrointestinal symptoms as previously suggested by Vaughan and Pipes.[2]

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2. Vaughan, W. T., and Pipes, D. M.: Is there a correlation between food dislikes and food allergy? J. Allergy, 8:257, 1937.

300 South Goodman St., Rochester 7, N. Y. (Dr. Glaser).
Submitted October 24, 1956

MEETING OF ACADEMY OF PSYCHOSOMATIC MEDICINE

The Fourth Annual Meeting of The Academy of Psychosomatic Medicine will be held at the Morrison Hotel, Chicago, Illinois, October 17-19, 1957. Although the three-day program is entitled "The Psychosomatic Aspects of Obstetrics, Gynecology, Endocrinology and Metabolism," the psychosomatic aspects of allergy, anesthesiology, dermatology, internal medicine, pediatrics, proctology and neuropsychiatry will all be discussed. An important panel will concern itself with Goals and Therapy in Psychosomatic Disorders. Twenty-four Round Tables have been assigned among others to the subjects of Migraine, Obesity, Ataractic Drugs, Comprehensive Therapy by the Non-Psychiatrist, and Endocrines and Emotions. A partial list of speakers includes Leonard H. Biskind, L. W. Sontag, Edmund Bergler, Edith Jackson, Sandor Rado, Harold Rosen, and Philip Thorek.

There is no registration fee. Applications for membership may be obtained from the Secretary, Dr. William S. Kroger, 104 South Michigan Avenue, Chicago 3, Illinois, or from the President, Dr. Ethan Allan Brown, 75 Bay State Road, Boston 15, Massachusetts.

ALLERGY AND THE DIFFUSE COLLAGEN DISEASES

N. G. B. McLETCHIE, M.D.
Laconia, New Hampshire

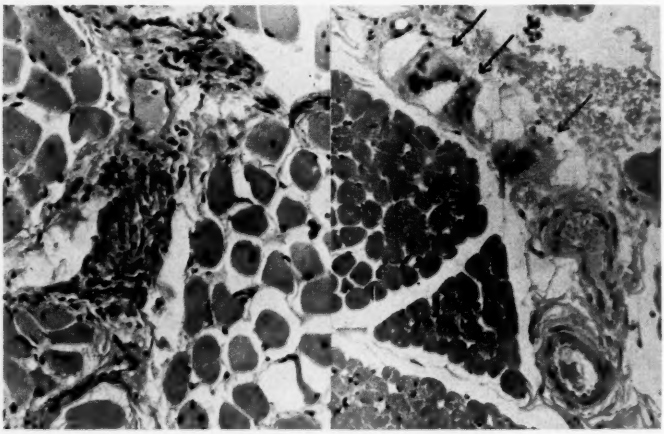
WITH the advent of cortisone and other therapeutic steroids, interest in the collagen diseases has increased. My interest began in a tangential fashion. Staining tissues is not only part of my work, it is also my hobby, and for many years I have played with the problem of reversing Gram's stain. Gram's stain for bacteria also stains fresh fibrin in tissues dark blue, almost black. Fibrinous infiltrates in tissues appear to undergo a gradual metamorphosis so that it is difficult to give precise definition to the material, either with Gram's stain or with any other routine laboratory stain. I have long tried to improve methods to recognize fibrin in its metamorphosis, and also to devise a method whereby the fibrin and its altered products would be uncolored with all the rest of the connective tissue stained intensely. This recognition of fibrin in sections is a topical problem. Fibrinoid necrosis of connective tissue is the hallmark of the collagen diseases. In this condition connective tissue cells generally first increase, and then the connective tissue becomes swollen, disorganized, and eventually amorphous. Dead connective tissue cells are incorporated in the amorphous mass, and sometimes also dead cells of inflammatory origin. The swollen and fused products take on the ordinary routine stains for fibrin—fibrinoid necrosis, but there is no agreement that fibrin is actually incorporated in the mass as the staining reactions are not regarded as specific. In the acute collagen diseases, fibrinoid necrosis of connective tissue is associated with a variable inflammatory response, and with vasculitis.

There are two extremes of vasculitis, proliferative and degenerative. In proliferative vasculitis, blood vessels show proliferation of the cellular elements of their walls, and often a perivascular cuff of cells derived from the fertile mesenchyme surrounding the vessel wall (Figs. 1 and 2). The proliferating mesenchymal cells may be undifferentiated, may differentiate to cells such as lymphocytes, or may form sarcoid-like accumulations of histiocytes. There is also a variable emigration of leukocytes into the tissue, and sometimes eosinophils predominate.

In degenerative vasculitis there is fibrinoid necrosis of the vessel wall (Fig. 3). Mixtures of both types of reactions are seen. Despite the inflammatory reaction and often necrosis in the vessel wall, thrombosis is exceptional so that the reaction presumably involves the activation of a potent thrombolytic mechanism. The vascular lesions are focal, and the involved vessels vary from medium muscular arteries right down and

Presented as a postgraduate lecture before the Medical Societies of Prince Edward Island and Saint John, New Brunswick, Canada.

through the arterial system to capillaries and veins. Commonly only one type of vessel is involved, but in some cases vessels of many types are involved.



Figs. 1 and 2. Proliferative vasculitis as seen in dermatomyositis. Figure 1 shows a small vessel with budding of endothelium into the lumen and a perivascular cuff of inflammatory cells. Figure 2 shows a small vessel (arrows) obliterated by proliferation of cells. (Hemalum and eosin.)

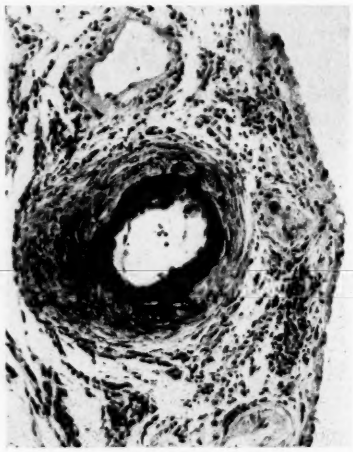


Fig. 3. Degenerative vasculitis as seen in polyarteritis nodosa, choroid of eye. The necrotic arterial wall is engulfed in fibrin (dark material). (Iodine-Mallory.)

Vasculitis, a variable inflammatory response, and fibrinoid necrosis of connective tissue form the morbid basis of the acute collagen diseases, and

also the tissue reactions of anaphylactoid allergy when it is sufficiently exalted to produce focal lesions. Indeed, it is in the latter group that the triad of changes is most frequently encountered by the pathologist.

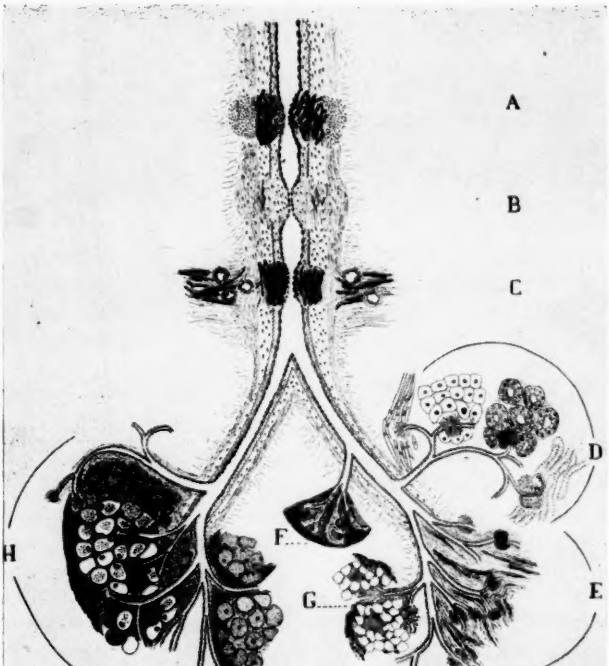


Fig. 4. Allergic vasculitis. The intense dark areas represent fibrinoid necrosis of connective tissue. A. Polyarteritis nodosa; focal areas of damage in muscular vessel. B. Polyarteritis nodosa of proliferative type. C. Allergic granuloma; surrounding small vessels and fascia are also involved. D. Arteriolitis allergica; disseminated microagranulomata in many organs and tissues essentially as a perivasculitis. E. Nodular vasculitis; fibrinoid necrosis and vasculitis, proliferative and degenerative, in foci of the integument, especially of the legs. F. Papulo-necrotic tuberculide; a small superficial infarct associated with intense vasculitis and fibrinoid necrosis. G. Weber-Christian disease; vasculitis and fibrinoid necrosis associated with fat necrosis. H. Dermatomyositis; variable vasculitis as in A-G, fibrinoid necrosis of connective tissue, lysis and hyalin necrosis of muscle.

MORPHOLOGIC DECLENSION

For this part I wish to descend the arterial tree beginning with muscular arteries, and to define the entities which *par-excellence* exhibit the triad of vasculitis, fibrinoid necrosis of connective tissue, and a cellular response.

This is illustrated diagramatically in Figure 4, where the fused black areas represent fibrinoid necrosis.

Polyarteritis Nodosa.—There are focal lesions involving the triad of lesions in the arterial wall. The target organ is medium and small muscular arteries, though arterioles may also be involved. Lesions are generally widespread, but exceptionally may be segmentally distributed, e.g., the lesions may be entirely confined to the kidneys. The acute reaction usually occurs over a short period of time so that all the lesions are of the same age (Fig. 3).

There is a proliferative type of polyarteritis nodosa, which may occur *ab igne* or represent a healing stage of this disease.

Allergic Granuloma of Asthma.—This condition is similar to polyarteritis nodosa except that the target organ is largely limited to a few segments of the arterial tree. In the involved segment, the lesions are still focal but involved all levels of the tree out to veins, and, unlike polyarteritis nodosa, the surrounding connective tissue shows intense fibrinoid necrosis. As a result large swellings are produced, and they slough like infarcts. Like polyarteritis nodosa, the noxious mechanism acts over only a short period of time. The lesion is only encountered in people with a long history of asthma. It is the natural homologue of the experimentally produced "Arthus phenomenon" in the rabbit, which is an exalted anaphylactoid reaction.

Arteriolitis Allergica.—The lesions are similar to the allergic granuloma of asthma, but in miniature. Microgranulomata with a central arteriole showing fibrinoid necrosis are found widely distributed in many organs and tissues. The condition is found in severe cases of serum sickness and drug allergy of the serum-sickness type. So-called thrombotic thrombocytopenic purpura is possibly a variant of this condition where microgranulomata are found with fibrin plugs in small vessels (Figs. 5 and 6).

Nodular Vasculitis.—Lesions are similar to arteriolitis allergica but are much more localized in distribution and may be confluent. The subcutaneous tissue of the legs, particularly the panniculus, is the commonest site. The clinical conditions encountered under this group are variously described as nodular vasculitis, erythema induratum, localized scleroderma (morphea), papulonecrotic tuberculide, some nodular forms of phlebitis, Weber-Christian disease, and drug rashes. Authors of textbooks and clinicians have difficulty in deciding boundaries between the conditions, and when in textbooks an attempt is made to differentiate the conditions in terms of their morphology it makes for heavy reading. Indeed, from case to case, and sometimes in any one case, there is a continuous spectrum of variation in quality and quantity of vasculitis, connective tissue damage, and inflammatory cellular response. The vasculitis may be mainly degen-

erative or proliferative, and variable as to the level of the vascular tree involved, the connective tissue damage varies from proliferation to intense fibrinoid necrosis. The cellular response may be almost absent, there may

Figs. 5 and 6. Allergic vasculitis of panniculus, showing small vessels with prominent endothelium and perivascular cellular cuffs (Fig. 5). There is also granular disintegration of collagen. A septum seen in the figure is enlarged to show the granular character (Fig. 6). (Hemalum and eosin.)

be marked leukocytic infiltration in which eosinophils may predominate, there may be proliferation of sarcoid-like follicles.

Papulonecrotic Tuberculide.—Alone of this latter group, papulonecrotic tuberculide has distinctive morphologic and clinical attributes. It occurs as small segmental and superficial foci of intense fibrinoid necrosis of connective tissue and vasculitis so that a papule forms, turns black and shows umbilication, then sloughs and heals. It is a replica in miniature of the focal intensity of the lesions of allergic granuloma of asthma, but it also differs in that it occurs in successive crops.

Weber-Christian Disease.—This is a clinical entity where foci of nodular vasculitis occur in successive crops in the panniculus. The lesions from case to case show the morphologic variations encountered in nodular vasculitis, and the relapsing febrile character alone gives it some distinction.

ETIOLOGY

The lesions which I have described form a continuous series in morphologic declension. They merely vary as to the site and distribution of the target organ. Moreover, within any one group the same range of variation in the three reactions, vasculitis, fibrinoid necrosis, inflammatory response, are encountered. Thus, while I mentioned sarcoid-like lesions in nodular

vasculitis, and did not mention them in relationship to polyarteritis nodosa, I have encountered one case with the classic lesions of polyarteritis nodosa in medium muscular vessels in which the cellular perivascular cuff consisted of sarcoid-like follicles. Thus, all of these diseases constitute a single morphologic group. Apart from the variation in symptoms due to the variable target organs and conditioned by whether the acute process is transient or relapsing, I do not consider that the group can be differentiated on other clinical grounds. When the lesions are sufficient in total extent to account for a large volume of tissue, there is almost always fever, anorexia, malaise and leukocytosis. Where the lesions are more confined, constitutional reaction is less obvious, and may be absent. Where the lesions are of long standing, there is generally alteration of plasma proteins. Hypertension is common in polyarteritis nodosa; it may be encountered in nodular vasculitis. Involvement of the nervous system is countered in polyarteritis nodosa but microgranulomata similar to nodular vasculitis are encountered in the brain in allergic encephalitis. While polyarteritis nodosa is usually acute with clamant presenting symptoms, it may be silent, and sometimes localized largely to the kidneys. Thus, in terms of pathology and symptomatology we have little grounds for not believing that we are dealing with a common noxious mechanism variable as to target organ and the intensity of action.

When encountered, the diseases we have described either prove to be of allergic origin or the etiology remains obscure. The evidence, both clinical and experimental, is approaching completion that polyarteritis nodosa is an allergic reaction. Foreign serum, drugs and bacteria have all been implicated. In about half the cases encountered, there is a long history of asthma or other forms of allergy. Allergic granuloma is only encountered as a complication of severe asthma. Arteriolitis allergica is seen in serum sickness and some drug reactions. The range of diseases classified under nodular vasculitis, all of which we have encountered, and some many times, either turn out to be of unknown etiology or are manifestly allergic. Tuberculous infection, streptococcal infection, antituberculous drugs, antibiotics, fungal infections, chemical fertilizers, have all been variously implicated in some of our cases. On morphologic and etiologic grounds we have, therefore, good reason to look on all of these diseases as belonging to one group, the allergic vasculitides. The variation of target organ is a good subject for clinical research. It is still a mystery why only a minority of patients become allergic to streptomycin and PAS, and it is also a mystery why it should be variously manifest as polyarteritis nodosa, arteriolitis allergica, nodular vasculitis, allergic encephalitis, or merely a drug rash.

THE COLLAGEN DISEASES

It will be noted that under the allergic vasculitides, polyarteritis nodosa has been included, which is also taken to be a classic example of a collagen disease. Indeed, it is from here that we pass in morphologic declension

to the collagen diseases. Dermatomyositis is claimed as the rarest of the collagen diseases. It is characterized by an insidious onset, muscular weakness, brawny edema, puffiness of the face, especially noticeable about the eyes, variable skin rashes, low grade fever, and an absence of leukocytosis. I have studied nine cases of the disease in children. In the panniculus and muscle there is fibrinoid necrosis of connective tissue, vasculitis, and degeneration of muscle. The range of vasculitis covers the range encountered in allergic vasculitis. Like polyarteritis nodosa, the disease is usually manifest as one single attack. Unlike the gloomy prognosis in previous accounts, only two of our children died, and only one became chronic. The remainder made a remarkably complete recovery. While there is no doubt that the range of morphologic change in the connective tissue and blood vessels corresponds to the range in allergic vasculitis, the etiology of dermatomyositis is more obscure. In one of our cases, however, the onset was relatively abrupt, and followed the administration of sulpha drugs for stomatitis, suggesting an allergic reaction to the drug. In two cases there was an initial history of prolonged sore throat and, like acute rheumatism, one would think that the commonest origin is an allergic reaction to streptococcal infection.

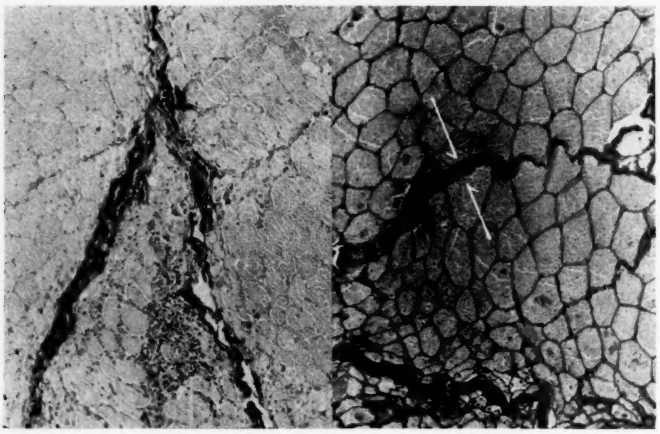
I do not intend to continue with a parade of the similarities and dissimilarities of morphology, clinical attributes and possible etiology in relation to the other collagen diseases—systemic lupus erythematosus, rheumatic fever, rheumatoid arthritis and scleroderma. In this country, the morphologic correlation has been dealt with fully by Lyman Duff. While there is a general acceptance that acute rheumatism is an allergic reaction to streptococcal infection beyond this disease, discussion will never be fruitful until we have more knowledge in regard to degeneration of collagen, and easier methods of approach to the study of allergy. It is an open question that in some of the collagen diseases which I have mentioned it is not so much the question of an abnormal antigen-antibody reaction (which is the basis of allergy), but rather that throughout life our tissues are buffering such reactions, and that in the latter group the defect is an inherent one of tissue response. That is to say, the tissues are inherently defective in response to a very wide range of immune reactions. While some may say that such a proposition holds for the whole field of allergy, it is noteworthy that in the first group, the allergic vasculitides, acute rheumatism and dermatomyositis, single extraneous etiologic factors, often avoidable or which can be combated, are becoming more evident, while in the second group the etiology remains obscure.

FIBRINOID NECROSIS OF CONNECTIVE TISSUE

Reactions of anaphylactoid allergy, to which so much of this discussion is germane, are held by the physiologist to result from an antigen-antibody union on tissue surfaces by virtue of which histamine is liberated, a proteolytic system is probably activated, and antithrombogenic substances

are liberated. This does not clash with the pathologic concept of vasculitis without thrombosis, and degeneration of collagen.

With the present popularity of the collagen diseases as a subject for



Figs. 7 and 8. Dermatomyositis. In Figure 7, a connective tissue septum shows fibrinoid necrosis stained black as for fibrin (Saline-Gram). At a later stage this inspissates and reforms as a septum of hyalin. This is shown in Figure 8 (Reverse Gram) where only connective tissue is stained. The arrow points to a hyalin fiber (unstained) containing scanty connective tissue fibrils (black).

discussion, it should be recognized that fibrinoid necrosis of collagen is still a very debatable subject among pathologists. The earliest change seen is a granular disintegration of collagen fibers so that the fibers are still in alignment but are broken down into granules. Beyond this there are all stages of dissolution until one is left with an amorphous "liquid" infiltrate, which appears to flow into the interstices of the tissue. Once advanced, the swollen disintegrating tissue takes on intensely the ordinary routine staining reactions for fibrin, which many regard as not being specific. Thus, there are may who deny that fibrin plays any part. Admittedly with some imagination one can trace the following sequence of events in dermatomyositis (Figs. 7 and 8):

1. The collagen becomes swollen and disorganized in architecture, but still gives the staining reaction for collagen. Sometimes the constituent fibrils of the fibres are unmasked and appear broken down and granular.
2. The swollen debris appears liquid, and takes on the ordinary staining reactions for fibrin.
3. The liquid infiltrate condenses and takes on once again the alignment of a collagen fibre, but still stains intensely as for fibrin.
4. This staining reaction is progressively lost so that the swollen fibre appears pale and glassy, and stains feebly but with the tinctorial reactions

as for collagen. In pathologic parlance, the connective tissue would be described in very general terms as a hyalin.

5. By special methods one can eventually recognize the constitutent fibrils of collagen (reticulin) being laid down in the hyalin matrix.

I prefer at this stage to consider that the fibrinoid element is indeed fibrin. It would appear then that we have an adaptive mechanism by which swollen disintegrating collagen is cast in its own image by an adsorption of fibrin from the blood, and that by virtue of this a temporary connective tissue, a hyalin, is constituted.

In the first place there is common sense in this approach. In polyarteritis nodosa, the acute necrosis of connective tissue would lead to rupture of the wall, and obviously this is prevented by "fibrinoid." The "fibrinoid" in the early acute stage gives intense reactions for fibrin. It is also sometimes so bulky that it is difficult to believe that much of the bulk does not come from the blood. Secondly, there is evidence of metamorphosis of fibrin to hyalin in other pathologic conditions, in the walls of chronically inflamed bursae, in the base of gastric ulcers, and in the stroma of tumors with an unstable vasculature, and in the organization of fibrin deposits on the intima of arteries one can often trace such a sequence of events. Thirdly, in therapeutic irradiation reactions, one frequently encounters the combination of vasculitis and fibrinoid necrosis of connective tissue as in allergic vasculitis and the acute collagen diseases. Earlier reactions show vascular dilatation and escape of serum into the tissues. Whatever be the truth this offers an easily controlled experimental approach to the problem. At present with a little imagination and the ordinary tools of histology, it is difficult to abandon the idea that irradiation does not activate a proteolytic system which breaks down the collagen while a fibrinous infiltrate of the blood casts the disintegrating collagen in its own image as an adaptive mechanism to provide temporary support.

HISTOCHEMISTRY

The pathologist in his routine studies fixes tissues as uniformly as possible, and uses largely empirical staining methods analyzing the tinctoral reactions of the unknown in terms of the reactions of known elements in the tissue. In recent years, histochemistry has made more advance. It is more precise in analysis, in that the staining reactions used are more defined chemical processes by which various elements in the tissue can be separated as to their chemical constitution. Histochemistry, optical methods of the physicist and electron microscopy have all been employed in recent years in the analysis of connective tissue lesions in the collagen diseases.

Nodules from rheumatoid arthritis have been commonly employed. In such nodules one can recognize, by ordinary staining methods, normal collagen, hyalin connective tissue, fresh fibrinous infiltrates, and fibrinoid

necrosis. The nodule is not inanimate. It is a living thing undergoing constant change. Thus, by any method of analysis, interpretation of results requires care. It is no wonder that, as yet, there is no general agreement as to the nature of fibrinoid necrosis.

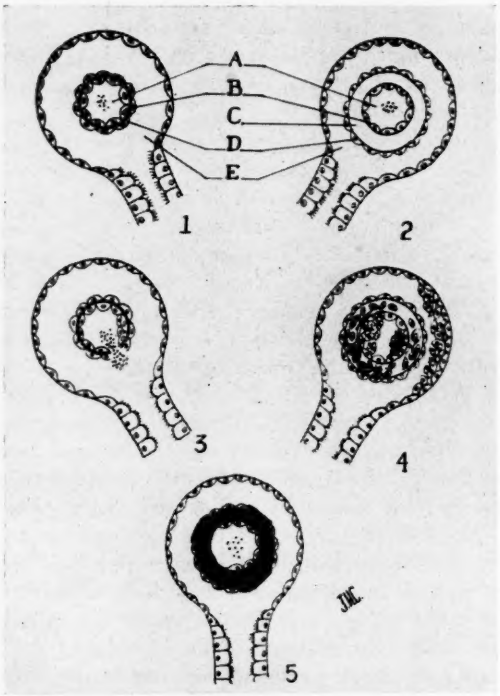


Fig. 9. The morphology of glomerulonephritis. A. The capillary lumen. B. The endothelial lining. C. The pericapillary space. D. The covering epithelium. E. The glomerular space. 1. Normal glomerulus. 2. The pericapillary space opened up. 3. Acute hemorrhagic glomerulonephritis. 4. Proliferative glomerulonephritis (Type 1—Ellis). 5. Membranous glomerulonephritis (Type 2—Ellis). The swollen capillary is cast in fibrin.

ALLERGY AND GLOMERULONEPHRITIS

The evidence, both experimental and clinical, is approaching completion that glomerulonephritis is an allergic reaction involving a morbid union of antigen and antibody within the glomerular capillary framework. If this is so, glomerulonephritis should demonstrate the morphology of allergic vasculitis at a capillary level modified by the special structures of the glomerulus. It is my purpose as a teacher to illustrate that this conception is the logical way to teach glomerulonephritis.

In Figure 9, the glomerulus *1* has been simplified to a single capillary

covered by epithelium, and surrounded by the glomerular space. In *2* the potential (pericapillary) space between the basement membrane of the endothelium and the covering epithelium has been opened up. Mild anaphylactoid reactions are characterized by erythema, edema, and simple

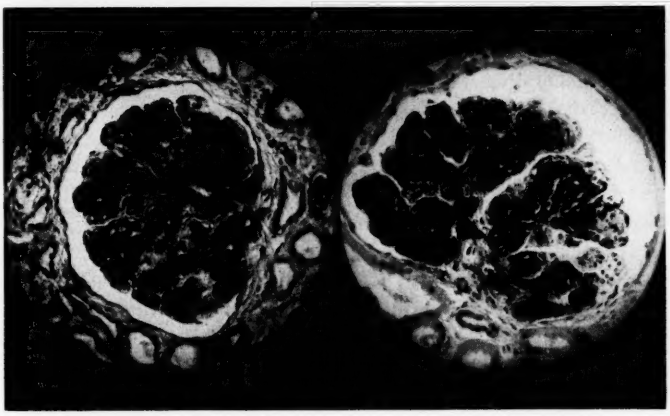


Fig. 10 (A)

Fig. 10 (B)

Fig. 10. Glomeruli from Type 2 nephritis. (A) Routine trichrome stain (Masson) shows cellular glomerulus with soft fibrinoid swelling (fused appearance) of the framework. (B) Staining for "fibrinoid" (Saline-Gram) shows heavy deposit (black) hardly suspected with previous routine stain. With Reverse-Gram (C) the fibrinoid is quite unstained, showing increased connective tissue fibrils. Using suitable controls, about one-fifth of the black material in (B) was shown to be fresh fibrin. The rest did not hold the reactions of fibrin to full differentiation, likely due to metamorphosis of fibrin. Therefore, the abnormal material of Figure 3 (polyarteritis nodosa), Figure 7 (dermatomyositis), and Figure 10(B) (Type 2 glomerulonephritis) is the same.

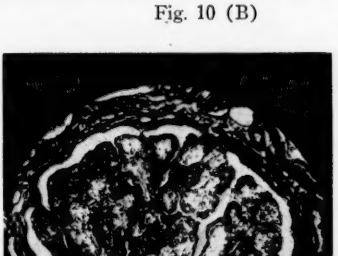


Fig. 10 (C)

purpura. In *3* no doubt this minimal vasculitis (leaky capillaries) is homologous with the condition usually described by pediatricians as acute hemorrhagic glomerulonephritis, where there is a transient clinical condition of mild glomerulonephritis accompanied by albuminuria and marked hematuria. In *4* there is illustrated the common form of severe glomerulonephritis. The glomerulus is cellular. The inflammation is a capillaritis characterized by proliferation of endothelial cells, and by mesenchymal

cells in the pericapillary space. There is variable fibrin infiltration. Fibrin thrombi may be encountered but are exceptional, illustrating the combination of proliferative vasculitis, and an antithrombic mechanism as in anaphylactoid allergy. The reaction at a capillary level is homologous with proliferative vasculitis as encountered in the generality of allergic vasculitides.

At the other extreme of anaphylactoid reactions in the vascular tree, there is degenerative vasculitis. Its homologue in the glomerulus, if anaphylactoid allergy has a morphologic equivalence in glomerulonephritis, should show capillaries with walls thickened and replaced by "fibrinoid," but basement membranes (mucopolysaccharide) should be intact if the reaction is essentially proteolytic. Despite the gross capillary lesion, the antithrombic mechanism should maintain a channel for the circulating blood. Lesions of this type are, in fact, encountered and variously described as the intercapillary type of glomerulonephritis, nephritis-type 2 —Ellis, and more recently membranous glomerulonephritis by Allen. The staining reactions which I have employed show the same range, suggesting that the reaction involves a metamorphosis of fibrin to hyalin. I find basement membranes to be intact, and the infiltrate is in the pericapillary space (Fig. 10). This is illustrated in *5* in the figure. What ever be the ultimate analysis of fibrinoid, there is no doubt that the analogy with allergic vasculitis is sufficiently complete as to conveniently teach the subject in the general conception of the allergic vasculitides.

I have looked at allergy and the collagen diseases from the viewpoint of the morphologist. While the morphologist's world is more restricted than the clinician's, the very restriction of the variables with which he deals is sometimes capable of enunciating fundamental propositions. Long ago, Klinge identified fibrinoid necrosis with allergy. The teaching of the physiologist is that the reactions of anaphylactoid allergy are proteolytic, thrombolytic, and histaminic, and one can see much of this teaching mirrored in the pathology of allergic lesions. Perhaps we are led on by wishful thinking, but at least it offers a basis of argument for those using methods of more precise measurement, and at the present limitations of our knowledge it offers a system of classification and understanding acceptable to reason.

Laconia Hospital

Submitted July 25, 1956.

"Nature nothing careth whether her abstruse reasons and methods of operating be or be not exposed to the capacity of men."—GALILEO GALILEI in the *Dialogues Concerning the Two Principal Systems of the World.*

PROVOCATIVE X-RAY THERAPY AS A NEW AID TO THE DIAGNOSIS OF SUSPECTED SINUSITIS

OSCAR SWINEFORD, JR., M.D., GEORGE COOPER, JR., M.D., and H. ROWLAND PEARSALL, M.D.
Charlottesville, Virginia

INFECTION in the sinuses is a frequent cause of asthma, chronic nasal symptoms and other syndromes. Clinical improvement depends upon the recognition and effective treatment of this infection. Diagnosis is usually easy. However, in an occasional case suspected sinus infection cannot be confirmed by conventional rhinologic and roentgenologic examinations.

The usefulness of radiation therapy in the treatment of sinusitis in children has been thoroughly explored.[1-3] In some patients receiving radiation, the initial small dose of 50 to 100 r causes purulent nasal discharge or a flare-up of hay fever or asthma. Though the mechanism is not very clear, the sequence of events in these patients is the appearance or intensification of symptoms within a few hours to several days after exposure to x-radiation. This observation led to the idea that the reaction to a relatively large single dose of radiation might confirm the suspected diagnosis of sinus infection in adults. It was assumed that subclinical sinusitis would be unmasked by a provocative dose of x-radiation. If this occurred, vigorous treatment of the sinuses would be justified.

The results of provocative x-ray treatment as a diagnostic procedure in forty patients, in whom sinus infection was suspected but not established by conventional clinical means, is the subject of this report. All of these patients had responded poorly to prior management. In most of the cases, consulting rhinologists had reported no significant sinus infection and that no sinus therapy was indicated.

METHOD

The provocative x-ray test consisted of a single dose of 200 r in air, (half value layer 1 mm Cu) to an anterior facial portal. The eyes and brows were shielded. In a few instances, more or less than 200 r was given early in the series, but 200 r was finally adopted as the standard dose. The effects of this single dose were evaluated within a few days.

Reactions were considered positive if either or both of the following occurred within twenty-four to seventy-two hours after the test: (1) purulent nasal discharge; (2) definite exacerbation of a major complaint, such as hay fever or asthma; or (3) troublesome cough, headache, or malaise.

From the Allergy-Arthritis Division, Department of Internal Medicine, and the Department of Radiology, University of Virginia School of Medicine, Charlottesville, Virginia.

SELECTION OF PATIENTS

The test was used in thirty-seven adults and three children, in each of whom the history suggested sinus infection. In most, inspection of the nose and throat, transillumination and roentgenograms of the sinuses provided suggestive, but never definite, evidence of sinus infection.

RESULTS OF FORTY PROVOCATIVE X-RAY TREATMENTS

There were fifteen positive reactions. Four were equivocal and twenty-one were negative. The reactions occurred within twenty-four hours in thirteen, and within seventy-two hours in two cases. The reactions which followed the provocative x-ray dosage in the fifteen positive cases are summarized in Table I.

TABLE I. CLINICAL MANIFESTATIONS OF POSITIVE REACTIONS

Increase in purulent or bloody nasal discharge	11
Hay Fever	10
Asthma or cough	5
Headache	7
Malaise	5

The incidence of clinical criteria suggesting sinusitis is shown in Table II. The incidence of each of these criteria in the whole group of forty cases is compared with the incidence of the criteria in those who had positive, equivocal or negative reactions to the provocative x-ray dosage. Note that none of the criteria correlated with the positive or negative reactions to therapy.

TABLE II. INCIDENCE OF EVIDENCE OF SINUSITIS
WHOLE GROUP VS. POSITIVE, EQUIVOCAL AND NEGATIVE REACTORS

Evidence for Sinusitis	Whole Group	Positive Reactors	Equivocal Reactors	Negative Reactors
History positive	40	15	4	21
Roentgenograms suggestive	26	9	3	14
Transillumination impaired	15	6	1	8
Inflammation of pharynx	18	5	1	13
Inflammation of nasal membranes	26	8	1	17

Antral lavage was done in eight of the positive cases and two of the equivocal cases, because history, local examination and/or roentgenography strongly suggested antrum infection. The returns were clear.

SUBSEQUENT TREATMENT

The fifteen patients who reacted to the provocative x-ray dosage were treated comprehensively for sinus infection. Nine improved satisfactorily. Six did not.

CASE REPORTS

The following three cases illustrate the effective diagnostic use of provocative x-ray therapy:

Case No. 1.—History positive, roentgenogram suggestive, local examination negative.

Mrs. A. P. P., aged forty-three, gave a history of perennial hay fever for twenty years. Recurrent transient bouts of acute rhinitis with mucopurulent nasal discharge began in midsummer 1955. Examination of the nose, throat, and sinuses was essentially negative. Treatment with antibiotics and nose drops did not help. Sinus roentgenograms showed slight haziness of the left antrum, ethmoid and sphenoid. The consulting rhinologist did not think specific treatment of the sinuses was indicated.

A provocative x-ray dose of 200 r to the sinuses was followed that night by a profuse purulent nasal discharge, a full, heavy feeling in the head, and extreme stuffiness of the nose. Three days later another dose of 200 r was given together with a short course of a sulfonamide and cortisone. She improved promptly. Her improvement has continued.

Case No. 2.—Asthma and sinus infection. The latter seemed to respond to antibiotics, but the asthma was not relieved until provocative x-ray disclosed latent persistent sinus infection.

Mrs. I. S., aged fifty-six, had had perennial, allergic and infectious asthma for nine months and recurrent episodes of mucoid and purulent discharge for three years. The antra transilluminated poorly. The nasal and pharyngeal mucous membranes suggested infection. Sinus roentgenograms showed underdevelopment of the left antrum. Three weeks of routine allergy management, plus antibiotics, resulted in almost complete disappearance of the purulent discharge, but little improvement in the asthma.

A provocative x-ray dose of 200 r was given to the sinuses. Within twenty-four hours there were abundant, thick, blood-tinged nasal discharges, plus headache and nasal burning. Her asthma was improved in three days. Fractional x-ray therapy was continued to the total air dose of 900 r. She passed thick, purulent nasal material with each additional treatment. Nasal decongestants, antibiotics and the allergy regime were continued. She continued to improve. Recent follow-up disclosed only one interim mild attack of asthma complicating a simple cold. The nasal discharge did not become purulent.

Case No. 3.—Chronic perennial hay fever, recent bouts of purulent nasal discharge, equivocal roentgenograms and local examinations.

Mrs. E. L. D., aged twenty-six, had suffered with perennial hay fever and asthma with seasonal exacerbations for four years. There were occasional bouts of purulent nasal discharge with negative physical examinations and negative roentgenograms. The response to an allergy program for several years was good. In 1955, short bouts of stuffy nose and purulent nasal discharge began, and the nasal mucosa suggested infection. The anterior sinuses transilluminated brightly and sinus roentgenograms were considered essentially normal. Equivocal changes in the antra and ethmoids were suggested. The consulting rhinologist did not think symptoms were due to sinus infection. A sulfonamide, antihistamines, and nasal decongestants provided no relief. A provocative x-ray dose of 200 r was followed in twenty-four hours by headache, a marked exacerbation of the stuffy nose, and a mucoid discharge which soon became thick and yellow. The reaction lasted three or four days. Following this, broad spectrum antibiotics plus nasal decongestants were followed by marked improvement. No treatment other than routine allergy measures have been necessary for six months.

SUMMARY AND CONCLUSIONS

Provocative x-ray therapy is, at times, a useful diagnostic procedure when sinusitis is suspected but necessary diagnostic criteria are lacking.

Forty cases suspected of sinus infection were given provocative x-ray doses of 200 r in an effort to confirm the suspected diagnosis. The diagnosis was confirmed in fifteen of the forty cases. Nine of the fifteen cases which reacted positively, or 22.5 per cent of the whole series, were relieved of their major complaints promptly when the sinus infection was treated comprehensively.

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ANAPHYLAXIS AND ANTI-ANAPHYLAXIS

What invests these anaphylactic phenomena with so mysterious a character is the fact that they are set up by substances that are entirely anodyne in nature. This upsets our ideas as to the harmfulness of the reverse of the substance. For instance, we inject an animal subcutaneously with an extremely weak, almost infinitesimal dose of milk or egg-albumen. Six months or a year later the same guinea-pig is inoculated with a dose of milk or egg-albumen that would not cause a normal guinea-pig to move a muscle. Barely two to three minutes have elapsed from the time of operation before the animal becomes overwhelmed. What is so astonishing is the fact that non-toxic substances assume so formidable toxicity in animals that have already been injected on a single occasion. What again is perplexing to the last degree is that substances such as egg-albumen, milk, and serum, which may be employed in almost unlimited quantities on ordinary occasions, become deadly in doses that are almost infinitesimal during periods of anaphylaxis.

Such is the riddle which numerous scientists have sought to explain. What is the source of this toxicity which nothing justifies and which nevertheless makes its appearance with such suddeness and violence at the time of reinjection of the same substance?

Clearly this toxicity can only originate in some change that takes place in the body of the animal itself under the influence of the first injection.—A. BESREDKA, M.D.: Anaphylaxis and Anti-Anaphylaxis and their Experimental Foundations (1919).

TRIPELENNAMINE HYDROCHLORIDE AND CHLORPROPHENPYRIDAMINE MALEATE

A Comparison of Their Efficacies in the Treatment of Hay Fever

CHARLES M. BANCROFT, M.D.
Wilmington, Delaware

THERE are two methods by which antihistaminic agents may be evaluated for efficacy: the most common is a simple determination of the degree of relief given each patient by a specific therapy (individual efficacy); less common is a determination of how the individual efficacy of one therapy compares with the individual efficacy of another (relative efficacy). Of the two, relative efficacy is probably the more important since a therapy which gives degrees of relief is not an absolute success or failure, it is only better or worse than other therapies.

Unfortunately, an evaluation of relative efficacy cannot be made by comparing the data obtained in separate studies of different medications. As Brown and Krabek[1] point out, "Papers which deal with clinical evaluations concern data which cannot be reproduced excepting within very wide limits" since, among other reasons, the "method of clinical evaluation varies with each physician who has his own interpretation of the patient's necessarily subjective report." As a result, there are as many different assessments of each antihistaminic agent's individual efficacy as there are clinical investigations. For example, chlorprophenpyridamine maleate and tripelennamine hydrochloride, two of the most widely used antihistaminic agents are reported in different studies as aiding from below 70 per cent to above 90 per cent of the patients treated.[2-5]

Obviously, the individual efficacies of antihistaminic agents cannot be compared to determine the relative efficacies of the medications unless the data have been obtained in the same study—one group of patients must be given the different medications under the same conditions and for the same disorder. The following double-blind, statistically balanced study of the individual and relative efficacies of chlorprophenpyridamine maleate and tripelennamine hydrochloride in the treatment of ragweed hay fever attempts to fulfill these rigid requirements.

METHOD

The following regimens were followed in this double-blind study:

1. Chlorprophenpyridamine maleate—sustained release capsule*
   Morning and Night: One 12 mg sustained release capsule plus one placebo tablet.
   Noon: One placebo capsule plus one placebo tablet.

Dr. Bancroft is an Associate Fellow of The American College of Allergists.

*"Teldrin" Spansule Capsules, Smith, Kline and French Laboratories, Philadelphia, Pennsylvania.

2. Tripelennamine hydrochloride—delayed action tablet**

   Morning and Night: One 50 mg delayed action tablet plus one 50 mg regular capsule.

   Noon: One placebo capsule plus one placebo tablet

3. Tripelennamine hydrochloride—regular dose.

   Morning, Noon, and Night: One 50 mg regular capsule plus one placebo tablet.

The sustained release dosage form of chlorprophenpyridamine maleate divides the medicament into many small, coated pellets. The pellet coatings vary in thickness and dissolve at different rates within the gastrointestinal tract. Part of the medicament is released immediately for a prompt effect while the remainder is released slowly and evenly to produce a sustained physiologic effect lasting from ten to twelve hours.

The delayed action tablet of tripelennamine hydrochloride employs an enteric coating which covers the entire amount of medicament. This coating delays the release of the medicament for about four hours. The delayed-action tablet is used in conjunction with a conventional tablet which releases the medicament promptly. By means of these two tablets, fast-acting and delayed-acting, a sustained physiologic effect is produced which lasts for approximately eight hours.

In order to reduce the complexity of the regimens used, and yet keep the study double-blind, the 50 mg regular dose of tripelennamine hydrochloride was made in capsule form and looked like the sustained release capsule of chlorprophenpyridamine maleate. Thus, by using a placebo capsule and placebo tablet, all three regimens could be set up so that a capsule and tablet were taken by patients three times daily.

Forty-five patients with ragweed hay fever were selected at random from private practice for this four-week study. All were adults; ranging in age from nineteen to fifty-six; twenty-two were men and twenty-three were women. All patients started therapy during the same week at the opening of the autumn hay fever season.

Each regimen was used by one-third of the patients each week so that by the end of the third week all forty-five patients had received the three regimens. Thirty-six of these patients participated in the study for the fourth week. During this week they repeated their first week's regimen.

Patients were examined each week and were given a supply of medication and a report card on which they checked the amount of discomfort they had experienced immediately before and one to three hours after taking each dose of medication. Discomfort was graded as "None," "Mild," "Moderate," or "Severe." Patients also graded the amount of relief they received during sleeping hours as "None," "Slight," "Moder-

**"Pyribenzamine" Delayed Action Tablets, Ciba Pharmaceutical Products, Inc., Summit, N. J.

ate," or "Complete." The report card also provided spaces for a day-to-day report of any side effects which might occur and for comments on the therapy's efficacy.

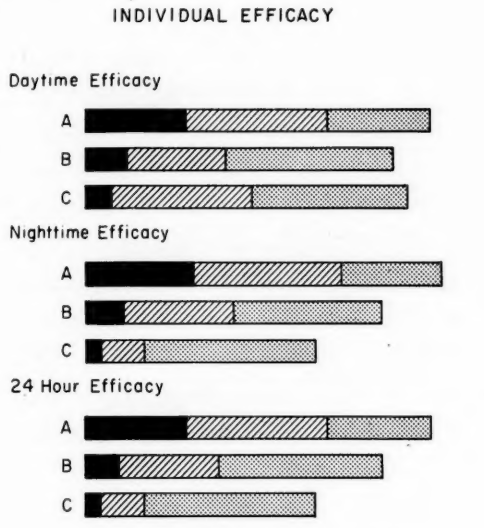

Fig. 1. Tripelennamine hydrochloride and chlorprophenpyridamine maleate—Individual Efficacy.

Results were scored for individual efficacy (the amount of relief given each patient by each therapy) and for relative efficacy (a comparison of the degrees of relief given a patient by each therapy). Individual efficacy was scored by assigning numerical values to the degrees of daytime distress and the amounts of nighttime relief recorded by the patients. The average difference between a patient's distress before and after medication was taken as the daytime efficacy of the therapy for the individual. Nighttime efficacy was obtained by averaging the amounts of nighttime relief recorded by the patient. The lesser of these two efficacies was taken as the twenty-four-hour individual efficacy of the therapy. The individual efficacies were then compared to determine the relative efficacy of each therapy.

RESULTS

Individual Efficacy (Fig. 1).—The sustained release capsule of chlorprophenpyridamine maleate was the most effective of the three therapies. It gave twenty-four-hour relief to forty-two patients (93.4 per cent).

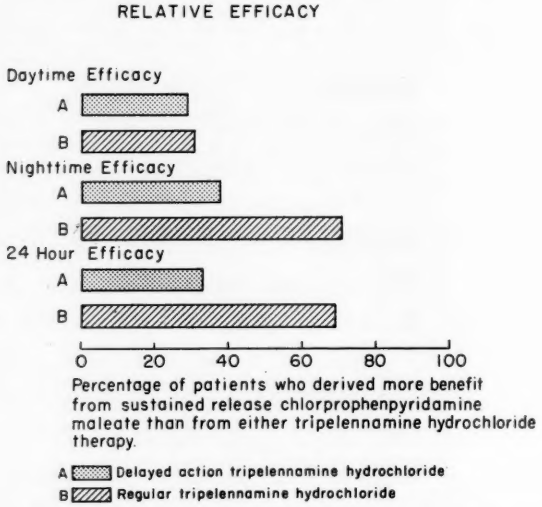

Fig. 2. Tripelennamine hydrochloride and chlorprophenpyridamine maleate—Relative Efficacy.

Next was the delayed action tripelennamine hydrochloride which gave twenty-four-hour relief to thirty-six patients (80.0 per cent). The regular (q 4-hour) dose of tripelennamine hydrochloride was slightly better during the day then the delayed action tablet, but its nighttime efficacy was much lower. Consequently, it must be considered the least effective of the three therapies. It gave twenty-four-hour relief to only twenty-eight patients (62.2 per cent).

Relative Efficacy (Fig. 2.)—During the day and at night more patients received a greater amount of relief when given the sustained release capsule of chlorprophenpyridamine maleate than when given either the delayed action or regular preparations of tripelennamine hydrochloride. A comparison of twenty-four-hour efficacies shows that of twenty-one patients who responded differently to sustained release chlorprophenpyridamine maleate and delayed action tripelennamine hydrochloride, eighteen (85.7 per cent) responded better to the chlorprophenpyridamine maleate. Of thirty-two patients who responded differently to sustained release chlorprophenpyridamine maleate and regular tripelennamine hydrochloride, thirty-one (97.0 per cent) responded better to the chlorprophenpyridamine

maleate. Of twenty-one patients who showed different responses to the tripelennamine therapies, nineteen (90.5 per cent) responded better to the delayed action dosage than to the regular one.

Agreement of Responses.—Thirty-six patients repeated their first week's medication during the fourth week of the study. There were very few differences between the patients' responses to medications the first and second time they received the therapies.

Untoward Reactions.—Seventeen patients exhibited untoward reactions to the therapies: Seven patients (15.5 per cent) under the sustained release chlorprophenpyridamine maleate therapy; nine (20.0 per cent) under regular tripelennamine hydrochloride therapy; and eight (17.8 per cent) under delayed action tripelennamine hydrochloride therapy. All untoward reactions were mild. The most frequent complaints under chlorprophenpyridamine maleate therapy were fatigue and dry nose or throat; under conventional tripelennamine hydrochloride, weakness, dizziness, and fatigue; and under delayed action tripelennamine hydrochloride, fatigue, weakness, dizziness, and poor appetite.

Patient Comments.—As might be expected, the day-by-day comments patients recorded agreed, on the whole, with their reports on discomfort and relief. Rather surprisingly, however, there was a great deal of similarity between the comments they made. Almost without exception patients referred to the inadequate nighttime protection given by regular (three times daily) tripelennamine hydrochloride therapy. Typical comments on regular tripelennamine hydrochloride are: "some relief by day, little at night," and "excellent day, fair night." In evaluating the delayed action tripelennamine hydrochloride and sustained release chlorprophenpyridamine maleate therapies, however, few patients differentiated between daytime relief and nighttime except in incidental comparisons such as: "slept better (on delayed action tripelennamine hydrochloride) than last week (when the patient received regular tripelennamine hydrochloride), and "didn't wake up sneezing" (when given sustained release chlorprophenpyridamine maleate).

DISCUSSION

The differences in efficacies of the three regimens were analyzed to determine whether those differences are statistically significant. As seen in Tables I and II, most of the differences between individual and relative efficacies of the regimens, as evaluated by the chi-square test, could occur by chance no more often than once in 100 times. Hence, the differences among the regimens can be considered highly significant.

It is interesting to note, however, that during the day the individual efficacies of the regimens are not significantly different (Table I) although

TABLE I. STATISTICAL ANALYSIS INDIVIDUAL EFFICACY

	Number of Patients			Chi_2^2	P
	Chlorprophenpyridamine Maleate Sustained Release Capsule	Tripelennamine Hydrochloride			
		Delayed Action	Regular		
Daytime					
Relief	42	37	39	2.56	.25
No relief	3	8	6		Not significant
Nighttime					
Relief	42	36	28	13.00	less than .01
No relief	3	9	17		Highly significant
24-hour					
Relief	42	36	28	13.00	less than .01
No relief	3	9	17		Highly significant

TABLE II. STATISTICAL ANALYSIS RELATIVE EFFICACY

	Number of Patients Obtaining Superior Relief			Chi_1^2	P
	Chlorprophenpyridamine Maleate Sustained Release Capsule	Tripelennamine Hydrochloride			
		Delayed Action	Regular		
Daytime	16	3	—	8.9	less than .01 Highly significant
	16	—	2	10.9	less than .01 Highly significant
	—	4	7	.82	.40 Not significant
Nighttime	18	3	—	10.7	less than .01 Highly significant
	32	—	1	29.1	less than .01 Highly significant
	—	21	2	15.7	less than .01 Highly significant
24-hour	18	3	—	10.7	less than .01 Highly significant
	31	—	1	28.1	less than .01 Highly significant
	—	19	2	13.8	less than .01 Highly significant

their relative efficacies show chlorprophenpyridamine maleate in sustained release capsule form to be significantly superior to either tripelennamine hydrochloride therapy (Table II). This seeming conflict in results occurs because an evaluation for individual efficacy cannot take into account the fact that while patients may be relieved by two different drugs, they may not receive the same amount of relief from both.

At this point the objection may be raised that degrees of relief are impossible to evaluate with any accuracy; what one patient may call "moderate relief," another patient may call "mild." The objection is valid, and to eliminate the difficulty, responses by one patient were not compared with those of another to determine relative efficacy. Instead, since each patient received all three therapies, the degrees of relief were compared only for the individual. Consequently, differences in criteria for judging degree of relief are not important. All that is important is that the individual be consistent in his use of his personal criteria. For this reason, the responses patients recorded the first and second time they received a therapy were analyzed to determined whether there was a differ-

ence between responses. A "T" test showed that there were no significant differences. Thus, it may be concluded that patients were consistent in using their personal criteria. Because of this consistency, and because the differences between responses to each regimen could happen by chance less than once in 100 times, the results may be accepted as being valid for the group treated.

CONCLUSIONS

The results show that one 12 mg sustained release capsule of chlorprophenpyridamine maleate given every twelve hours gives twenty-four-hour relief of ragweed hay fever symptoms to more patients, with a greater degree of relief to most patients, than does tripelennamine hydrochloride given either as one 50 mg regular capsule every four hours or one 50 mg regular capsule and one 50 mg delayed action tablet every twelve hours.

The findings also show that night-long protection is necessary for the allergic sufferer. This is borne out by the significant difference between the daytime and nighttime efficacies of regular (q 4-hour) tripelennamine hydrochloride. During the day, when the therapeutic effect of the drug could be maintained through a second dose at noon, the regular dose of tripelennamine hydrochloride was fully as effective as the delayed action (q 12-hour) tablet. At night, however, it was much less effective. It left many patients unprotected, and gave most of the others less protection than it did during the day. Presumably, a short acting tablet of chlorprophenpyridamine maleate would have the same defect of not giving sufficient protection at night and would prove as much inferior to the sustained release capsule (q 12-hours) as the regular tripelennamine hydrochloride is inferior to the delayed action tablet.

SUMMARY

Forty-five patients suffering from ragweed hay fever were treated with chlorprophenpyridamine maleate in sustained release capsule form (12 mg q 12-hours); tripelennamine hydrochloride in regular doses (50 mg q 4-hours); and tripelennamine hydrochloride in delayed action tablet (100 mg q 12-hours). Each patient received each therapy for one week. The study was both double-blind and statistically balanced to eliminate extraneous factors. The results of the study show:

1. Sustained release chlorprophenpyridamine maleate gives more patients a greater amount of relief than does either tripelennamine hydrochloride therapy.

2. The delayed action (q 12-hour) dosage of tripelennamine hydrochloride helps more patients at night than does the regular (q 4-hour) dosage of the drug.

3. The regular (q 4-hour) dosage of tripelennamine hydrochloride does not give adequate protection to most patients during the night. Presumably,

this inability to give adequate nighttime protection would be true of all q 4-hour dosages regardless of the drug given.

4. Few patients developed untoward reactions to the therapies, and all reactions were mild.

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1005 N. Rodney Street

Submitted September 18, 1956

THE ALLERGIC

An angel at the door can make them
sneeze,
or blue light breaking from a miller's
wing,
so nice is the disorder of their breath,
so wind-swept is the heart of everything.
Gazelles must keep in bounds, and
orioles
transport their gold combines to darker
trees;
the world of pelt and plume and naked
rose
is battered by the dust's duplicities.
The rain brings succor, but the rain is
brief;
behind it, like a horse, the black wind
rears
and gallops to their nostrils. Pity these,
who, when they weep, must weep with
dusty tears.

—Adrien Stoutenburg

Reprinted from *The New Yorker*, March 30, 1957, with permission of the publisher and the author.

CLINICAL EVALUATION OF SANDOSTENE®, A NEW ANTIHISTAMINIC DRUG, IN ALLERGIC DISEASES

Results of a "Double-Blind" Investigation

PHILIP M. GOTTLIEB, M.D., F.A.C.A., and
JACOB YANOFF, M.D., F.A.C.A.
Philadelphia, Pennsylvania

IT IS widely recognized that the ideal antihistaminic agent, one possessing maximal therapeutic effectiveness and minimal undesirable effects, is not available. This situation, plus the unpredictability of the clinical benefit from any one drug in any one allergic patient, has stimulated the search for new, and possibly superior, compounds possessing antihistaminic activity.

Sandostene,® a piperidine compound having the chemical formula 1-methyl-4-amino-N'-phenyl-N'-(2'thenyl)-piperidine tartrate, has been intensively investigated pharmacologically. It was found to occupy an intermediate position in histamine antagonism when compared with a large series of available antihistaminic substances.[21,22] It also exhibited low toxicity, in both acute and chronic experiments, marked anticholinergic and local anesthetic properties, and an inhibitory effect on tissue permeability in various types of experimental edema.

In view of these promising characteristics, Sandostene has been employed clinically, chiefly in the treatment of dermatologic conditions.[1,5,8-11,13,15-20,24-26] Most of the reports emanated from foreign investigators.[5,9,10,13,15-19,25,26] Of the clinical trials carried out in the United States, many were largely or completely restricted to skin diseases.[1,8,11,20,24] One American study was limited to pediatric patients.[7] Some of the reports included varying numbers of patients with nondermatologic allergies.[1,5,7-9,13,15,19,25,26] Many of these studies employed a combination of a calcium compound with the antihistaminic by oral administration, while others administered the combination intravenously, either to initiate therapy or in the more difficult cases. When Sandostene was given orally in addition to intravenous Sandostene-Calcium, 25 mg tablets were frequently used. (The results obtained by the present authors with the oral administration of a syrup containing Sandostene and calcium gluconogalactogluconate will be the subject of a future report.[14])

The varying dosage schedules and combinations employed by different investigators preclude a detailed summarization of the results. It appeared that Sandostene was clinically effective in the majority of patients with a variety of pruritic dermatoses, including urticaria, contact dermatitis, atopic dermatitis and pruritus ani et vulvi. A marked antipruritic effect was noted. Generally favorable results were observed in hay fever,[5,7,8,15]

From the Allergy Clinic of the Sidney Hillman Medical Center of the Male Apparel Industry of Philadelphia.

allergic rhinitis[7,9,15,17,25,26,29] and some cases of bronchial asthma.[1,5,7-9,13,-15,19,29] Other nondermatologic disorders in which benefit was noted included drug reactions,[1,5,17,19,26] nonhemolytic blood transfusion reactions,[13,23] allergic enterocolitis,[15,29] allergic conjunctivitis and keratoconjunctivitis,[15] and serum sickness.[19] It is also of interest that the drug provided significant protection against motion sickness in a controlled study.[6]

Serious side effects were not observed in combined reports encompassing several hundred patients, while most series revealed untoward effects of a type and with an incidence characteristic of other antihistamines.

No report has come to our attention in which a series of patients suffering from allergic diseases was treated with Sandostene alone (without calcium) and without employing the intravenous preparation. Accordingly, we decided to evaluate the drug by oral administration alone, determining the effects in a group of allergic patients by means of a controlled study. It was deemed necessary to employ a placebo for comparison, and also to administer, at a different time, another antihistamine of recognized efficacy, in random sequence.

It is admittedly difficult to determine accurately the effect of drugs on symptoms, or to assay the efficacy of drugs the effect of which is largely subjective. Numerous psychologic factors, the rapport between the patient and the investigator, the enthusiasms and beliefs of the latter, unconscious bias, and other uncontrolled and often unrecognized factors enter into such an appraisal. In order to eliminate these factors, the insertion of a placebo as an unknown in the experimental design is so widely accepted as not to require further justification.[2-4,12] Only by this means can the so-called "placebo-reactors" be detected and their spurious but nonetheless very real numerical influence on the quantitative results of the drug study be avoided. At the same time, each patient constitutes his own control, so that a parallel control series is unnecessary. However, it is not sufficient that only the patient be unapprised as to which is the active medication, but it is equally important that the reporter be similarly uninformed. Only when the clinical observations have been completed and all data recorded and correlated, may the investigator be made aware of the identity of each preparation. This, in brief, is the essence of the "double-blind" technique.[2-4,12]

METHOD

Ambulatory patients were selected for the study according to the following criteria. All were adults, with an average age of 47.3 years (range seventeen to seventy-four years). There were approximately equal numbers of male and female patients. They had been under observation for a sufficient length of time so that their symptoms could be considered

more or less stabilized. Aside from a few private patients, the observations were carried out on clinic cases. All were able to report results and submit to appropriate examination at least once a week and sometimes oftener. No other antihistaminic or anti-allergic medication was to be taken during the period of observation. Those patients already receiving subcutaneous hyposensitization with allergenic extracts (inhalants and/or pollens) continued this treatment.

White tablets* of identical size and appearance were prepared with the following constituents: (1) Sandostene, 50 mg; (2) tripelennamine hydrochloride, 50 mg; and (3) placebo (lactose).

The preparations were identified only by an uninformative code number. At the weekly visit, the selected patients were given thirty tablets of one of the preparations in randomized order and instructed to take one tablet four times daily after meals and at bedtime. A few patients took the tablets less often. By randomization of the sequence in which the tablets were administered to the patients, it was thought that the influence of meterologic factors and of fluctuations in the pollen count would be obviated, since at any one time, approximately equal numbers of subjects were taking each of the three preparations. At the next visit, the patient's appraisal of the medication was noted, and pertinent aspects of the physical examination (such as inspection of the skin in urticaria, examination of the conjunctival and nasal mucosa in rhinitis, or auscultation of the lungs in bronchial asthma) and the occurrence of any undesirable effects were recorded. A supply of the next drug was then given with the same instructions. This was repeated until each patient had taken all three preparations. He was then asked his preference for one of the preparations. The preference expressed did not invariably accord with the greatest therapeutic efficacy, being modified by a differential effect on various symptoms, by the nature and severity of side effects, and by other subtle influences. All interviews, examinations and recording were accomplished by the authors. The observations were carried out between March and November, 1955, including the 1955 hay fever season, which, judging from the pollen counts and general clinical experience, was a severe season in the Philadelphia area.

The results were considered excellent if the medication produced complete or more than 75 per cent relief of symptoms; good, between 50 and 75 per cent relief; fair, if between 25 and 50 per cent; and poor, if less than 25 per cent.

Only after all the data had been collated was the "key" opened to translate the code numbers into terms of chemical composition.

In all, 117 patients were started on the study. Of these, thirteen were lost to the clinic before completing the four visits required, and five were deliberately dropped from the study before completing the entire course,

*Kindly supplied by Mr. Kenneth Ericson, Research Department, Sandoz Pharmaceuticals, Hanover, New Jersey.

TABLE I. RESULTS OF TREATMENT OF ALLERGIC DISEASES WITH TABLETS OF SANDOSTENE, TRIPELENNAMINE, AND PLACEBO

Diagnosis	No. of Cases	Sandostene				Tripelennamine				Placebo			
		E	G	F	P	E	G	F	P	E	G	F	P
Bronchial asthma	10	3	1	3	3	1	2	2	5	1	2	2	5
Asthma and rhinitis	10	5	2	1	2	4	2	0	4	0	4	1	5
Allergic rhinitis	21	7	3	4	7	8	2	3	8	4	5	2	10
Hay fever	50	27	14	2	7	29	4	6	11	8	5	5	32
Chronic urticaria	8	4	2	1	1	4	0	1	3	1	2	0	5
Totals	99	46	22	11	20	46	10	12	31	14	18	10	57

Key: E = Excellent results, with complete or better than 75 per cent relief of symptoms;
G = Good results, with 50 to 75 per cent relief;
F = Fair results, with 25 to 50 per cent relief; and
P = Poor results, with no relief or less than 25 per cent relief.

because it was felt that their symptoms were not sufficiently severe, even without medication, to permit proper evaluation of the drugs. The remaining ninety-nine patients completed the entire course of the drug trials and constitute the group giving the results noted below.

RESULTS

The patients were classified according to usual diagnostic criteria into the five categories listed in the first column of Table I. The pollinosis cases comprised forty patients with weed (principally ragweed) hay fever, eight with grass, and two with tree hay fever. It was considered desirable to keep the entries of patients suffering from both bronchial asthma and allergic rhinitis separate from those with each disease alone. No cases of acute or short-term urticaria were included. The results of the drug trials in each diagnostic group as reported by the subjects, supplemented by the observers' impressions on physical examination, are given in Table I. The sex and age of the subjects, all of whom were adults, did not noticeably influence the results.

Notation was made regarding those patients receiving hyposensitization therapy. It was thought that this did not influence the study, since only those patients having troublesome symptoms despite the injections were included in the study, and since the injections were continued unchanged before, during, and after the trial period. Approximately two-thirds of the patients were receiving hyposensitizing injections.

As has been noted by others, a one-week trial of an antihistamine appears to be more than sufficient in order to establish an opinion regarding its efficacy in any one patient. Almost without exception, those subjects reporting favorable effects stated that they appeared within the first day, and frequently after one or two tablets. Most patients had no difficulty in giving their personal appraisal of the drugs, and many had very strong views.

An attempt was made to determine any differential influence on the specific symptoms of any one disorder. Accurate and orderly data were difficult to accumulate in this phase, but distinct trends appeared. When

TABLE II. PATIENT PREFERENCE REGARDING TABLETS OF SANDOSTENE, TRIPELENNAMINE, AND PLACEBO

Diagnosis	No. of Cases	Sandostene	Tripelennamine	Placebo	No Preference
Bronchial Asthma	10	4	1	1	4
Asthma and rhinitis	10	5.5	3.5	0	1
Allergic rhinitis	21	6	7.5	3.5	4
Hay fever	50	22.5	18.5	4	5
Chronic urticaria	8	5.5	1.5	1	0
Totals	99	43.5	32.0	9.5	14

Note: When a patient expressed equal preference for two preparations, 0.5 unit was credited to each o the preparations selected.

perennial allergic rhinitis and hay fever were benefited, the greatest effect appeared to be the control of sneezing and of nasal and ophthalmic pruritus, with nearly as much diminution in the nasal discharge, but somewhat less improvement in the nasal obstruction. Asthmatic patients reporting relief of significant degree often stated that the wheezing and to some extent the dyspnea were influenced more than cough, but one patient proved a notable exception. In urticaria, the pruritus was sometimes improved more than the whealing rash, but generally, both were controlled to an equal extent. In this symptomatic breakdown, no marked differences were noted between Sandostene and tripelennamine.

Although not properly part of a "double-blind" investigation, an effort was made to review the results in those patients not completing the course of all three tablets. While only relatively few cases were involved, the individual results did not greatly differ from the trends already noted.

Each patient was queried regarding his over-all preference for one of the medications after all three had been tried. Since each patient constituted his own control, the responses were deemed highly significant. They are tabulated in Table II. A few patients expressed equal regard for two tablets (sometimes, but infrequently, including the placebo) and this was noted. Fourteen patients, chiefly those obtaining poor results, refused to express a preference.

Examination of Tables I and II indicates that both antihistaminic drugs are quite effective in the therapy of hay fever, and reasonably so for urticaria and cases with both asthma and allergic rhinitis. The figures are to be compared with those for the placebo to obtain the proper impression. Less striking results were obtained in cases of asthma and of allergic rhinitis. Further analysis of the data, and a comparison of Sandostene with tripelennamine, are given below. When the hay fever cases were considered with regard to their season (tree, grass, or weed) no substantial differences appeared. As might be expected, patients with allergic rhinitis complicated by mucoid nasal polyps tended, on the whole, to report poorer results with any preparation than those without polyps. The same holds true of bronchial asthma complicated by pulmonary emphysema.

TABLE III. INCIDENCE OF SIDE EFFECTS ATTRIBUTED TO TABLETS OF SANDOSTENE, TRIPELENNAMINE, AND PLACEBO

Side Effects	Sandostene	Tripelennamine	Placebo
Sleepiness, drowsiness	16(5)	7(2)	5
Giddiness	3(1)	1(1)	—
Nausea	2(1)	1(1)	4(1)
Diarrhea	—	1	2(1)
Constipation	3	1	1
Abdominal cramps	—	4(3)	3(1)
Heartburn, flatulence, anorexia	1	5	3
Dry mouth or throat	8	4	—
Bitter taste	3	4	—
"Nervousness"	1	1	—
Tremor	1	1	—
Palpitation	1	1	—
Cough, "chokiness"	2	2	3
Headache	1	—	2(1)
Urinary difficulty	2(1)	2(1)	—
Miscellaneous	3	1	—
Totals	47(8)	36(8)	23(4)

Note: Numbers in parenthesis indicate the number of patients in whom the medication was discontinued because of the side-effects.

At each visit, the subjects were questioned in general terms concerning side effects. A determined effort was made not to suggest symptoms. The replies are given in Table III. The figures record individual complaints, so that the totals for each drug are somewhat greater than the number of subjects reporting such symptoms. The frequency with which the medication was discontinued because of troublesome symptoms is also indicated in Table III for each preparation. When this occurred, the patient was given the next medication in order. Since neither the patient nor the physician was aware of the constituents of the medication, any untoward symptom reasonably attributed to antihistamines was recorded. In retrospect, it is realized that some of these "side effects" were unrelated and coincidental, but no records were changed. The "miscellaneous" group included one case each of stinging in the mouth, blurred vision, and itching of the eyes for Sandostene, and an instance of early and unexpected menstruation ascribed to tripelennamine. The dysuria blamed on both antihistamines occurred in the same two male patients with some degree of prostatism.

No serious or alarming side effects occurred in any subject. All untoward effects disappeared within twenty-four hours and often much sooner, when the drug was discontinued. The sleepiness which constituted the most frequent undesirable symptom was usually of mild or moderate degree. The medications were discontinued, when necessary, largely as a precautionary measure, since most of the subjects worked with power machines in the clothing trade, and many drove automobiles.

STATISTICAL ANALYSIS

Both the tabulated data and the individual patient records were subjected to extensive statistical analysis by Dr. Stanley Schor of the Statistics Department of the University of Pennsylvania. Some minor variances

in details occurred depending on the precise method of analysis. The following statements are excerpted from Dr. Schor's report.

"If excellent and good results are grouped and tested against fair and poor results . . . for hay fever, both Sandostene and tripelennamine were significantly better than the placebo at the .01 level of significance but no significant difference (at the .05 level of significance) was observed between the two drugs. . . . The second method consists of ranking the drugs by order of effectiveness for each patient and testing these paired comparisons. . . . When the treatments were paired (i.e., with each patient becoming his own control), both Sandostene and tripelennamine gave significantly better results than the placebo for hay fever, but there was no significant difference between the effects of the two drugs. For asthma and rhinitis as well as for urticaria, Sandostene was significantly better than both tripelennamine and the placebo."

More refined techniques of analysis, including assignment of numerical values corresponding to the treatment results, and elimination of the placebo-reactors, led to substantially the same conclusions: "There is strong evidence that Sandostene is better than tripelennamine in the treatment of asthma and rhinitis; slightly weaker evidence that that is true when the diagnosis is urticaria. Both drugs are excellent in the treatment of hay fever, but neither was very good for rhinitis alone or asthma alone. . . .

"Analysis of the patients' responses concerning their preference indicated that both Sandostene and tripelennamine tablets yielded significantly more preference than the placebo for hay fever. Significantly more patients preferred Sandostene than the placebo tablet for asthma and rhinitis. For no diagnosis was there a statistically significant difference in preference between Sandostene and tripelennamine tablets."

DISCUSSION

The material presented in the two preceding sections would seem to indicate that Sandostene, a new antihistaminic medication, compares favorably with tripelennamine and other antihistaminic drugs in the treatment of a variety of allergic disorders. The nature of and incidence of undesirable effects were likewise comparable. The over-all clinical effects, the influence on specific symptoms, and the poorer results in patients with nasal polyps or pulmonary emphysema were all approximately as would be expected from an effective antihistaminic drug. As with all similar medications, the administration of this antihistamine is in no way a substitute for specific allergic diagnosis and specific therapy.

The authors have long felt that the antihistamines are ineffective in the treatment of bronchial asthma. It was decided to include asthmatic individuals in the series merely in the interests of objectivity. The fact that a number of them, especially those with both asthma and allergic rhinitis, reported improvement, particularly in comparison with the

placebo, proved somewhat surprising. It has long been recognized that allergic rhinitis and asthma are often present in the same patient.[27,28] In such individuals, when benefit was recorded, the improvement was by no means always confined to the nasal symptoms, but often referred as well as to the wheezing and dyspnea, and less so to the cough. On the whole, however, taking into consideration all subjects with asthmatic symptoms, these were helped less often than those with other allergic disorders.

The number of subjects attributing benefit to the placebo ("excellent" in fourteen, and "good" in eighteen cases out of a total of ninety-nine) is not surprising to any one who has employed placebos. The figures correspond quite closely with Beecher's[3] findings of a placebo effect of 35.2 ± 2.2 per cent in a wide variety of conditions. Likewise, the incidence and diversity of side effects blamed on a placebo is not uncommon when neither the subject or observer knows that only a placebo has been administered. Such findings have been repeatedly reported.[3,30]

Many observers have noted that individual patients are more likely to respond to one antihistaminic drug than to another. Differences in untoward effects are also common. This has led to the clinical practice of changing the antihistaminic medication when the patient fails to respond to the first drug tried. Accordingly, it is of value to have available an addition to the therapeutic armamentarium, giving the physician another choice of an unrelated chemical grouping.

It is superfluous to emphasize the points that rational therapeutics demands objective evaluation of drug efficacy, and that proper assessment of drugs influencing subjective symptoms requires the use of placebos and a "double-blind" method. Only by this means can the role of suggestion as a part of therapy be eliminated, as well as unconscious bias on the part of the observer. Beecher[3] has summarized this point: ". . . it should be apparent that 'clinical impression' is hardly a dependable source of information without the essential safeguards of the double unknowns technique, the use of placebos also as unknowns, randomization of administration, the use of correlated data (all agents are studied in the same patients), and mathematical validation of any supposed differences. These safeguards are essential when matters of judgment enter into decision." The present study has adhered to these recommendations.

SUMMARY AND CONCLUSIONS

1. Sandostene,® a new antihistaminic drug of the piperidine group, was subjected to clinicial trial by means of a "double-blind" technique, in comparison with tripelennamine and an inert substance (placebo), in a series of ninety-nine allergic patients.

2. In doses of 50 mg four times daily, Sandostene compared favorably in clinical benefit to tripelennamine in the same dosage.

3. With regard to specific diagnoses, greater benefit was noted when

either Sandostene or tripelennamine was used in cases of hay fever, urticaria, and patients with both asthma and allergic rhinitis, than in cases of perennial allergic rhinitis or asthma alone. A brief statistical analysis is presented. This indicated that Sandostene was significantly better than tripelennamine for asthma with allergic rhinitis as well as for urticaria.

4. Detailed review of specific symptoms revealed that within any one disorder, certain complaints were more likely to respond to antihistaminic medication than others.

5. No serious side effects were noted at this dosage level during the one week period. The type and incidence of the side effects were comparable to those produced by other antihistaminic drugs. All subsided promptly with discontinuance of the drug, as was necessary in eight cases.

6. Sandostene appears to be a useful addition to the antihistaminic series in the treatment of respiratory and dermatologic allergies.

7. The clinical evaluation of antihistaminic drugs and other drugs having principally symptomatic effect, can be properly accomplished only by a "double-blind" technique employing also a drug of accepted efficacy and a placebo.

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818 Medical Arts Building (Dr. Gottlieb)

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"It is the peculiarity of living things not merely that they change under the influence of surrounding circumstances, but that any change which takes place in them is not lost, but retained, and, as it were, built into the organism, to serve as the foundation for future action. . . . "—Ascribed to W. K. CLIFFORD, by SIR J. ARTHUR THOMSON and PATRICK GEDDES in *The Characteristics of Organisms* (1931)

Progress in Allergy

MISCELLANEOUS REVIEW OF ALLERGY

1956

LAWRENCE J. HALPIN, M.D.
Cedar Rapids, Iowa

The preparation of this annual miscellaneous review is always an arduous, but pleasant, task. The personal belief persists that the reviewer always gains more than the reader. An attempt has been made to avoid, as much as possible, the inclusion of those publications which rightly belong in a specific category. The material has been grouped into sections according to systems or symptoms. Subdivisions have been indicated to assist the reader in his use of the following paragraphs.

GENERAL CONSIDERATIONS

Serum sickness and the science of allergy.—Serum sickness is due to the parenteral injection of foreign protein. Schick[80] describes the incubation time as similar to that found in an endotoxic disease. Since serum is a dead substance and not in itself toxic, it contains no bacteria nor endotoxin and does not multiply. He and Pirquet, in their monograph published in 1905, theorized that horse serum is a foreign protein, is not tolerated when injected parenterally, and must be destroyed. This destruction must be carried out by the cells of all of the organs in the body. Since these organ cells are not as well prepared as the cells of the intestinal tract in the destruction of protein, they are only potentially able to mobilize antibody-like substances. The time required for the mobilization of these antibodies has been called the incubation period or the incubation time. Toxic intermediary substances are created during the interaction of antigen and antibody. Since these toxic substances are not readily detoxified, the symptoms of serum sickness ensue. These antibodies, once created, stay in circulation for about four months and then slowly disappear. If serum should be reinjected within this four months' period, it immediately interreacts with the still present antibodies; and no incubation time is required. When reinjection of serum takes place more than four months after the first injection, the interreaction between antigen and antibody can occur earlier than after the first injection. If these symptoms of serum sickness appear after four to six days following the injection of the serum, the reaction is stated to be accelerated. These immediate and accelerated reactions are intensive. They can be so violent that the patient may go into shock and may die. Pirquet recognized that the situation in infectious diseases was quite different. Here the mobilization of antibody against an infectious disease initiates the disease and leads, through the killing of the invading germ, to the end of the disease. Any reactions are beneficial and demonstrate clinical immunity. All allergic symptoms of rheumatic infection, collagen diseases, periarteritis nodosa, nephritis and many others follow the paradigma as serum sickness and are due to protein-containing substances. This mechan-

ism of defense does not bring about immunity. Schick has pointed out that the main features of allergy are part of a physiologic defense mechanism of nature and are beneficial to the patient.

In the fifty years since Von Pirquet's historic pronouncement allergy has become increasingly known to the medical profession and to the lay public. Most of the early pioneering work has been of European origin. However, Feinberg and Feinberg[31] state that subsequent clinical and experimental development of the field of allergy has been mainly an American accomplishment. They point out that recognition of specific causes of allergic diseases is on the increase. The diagnosis in allergy has as its objective the recognition of the syndrome as allergic, the recognition of the complications and the establishment of a specific cause for the disease. They emphasize that skin tests are important, but their proper use and interpretation in the consideration of the patient as a whole are even more important. They point out the importance of specific treatment in allergy as well as the specific elimination of causative factors. Desensitization to inhalant allergens has become a procedure increasingly accepted and has resulted in relief to hundreds of thousands of sufferers. Nonspecific treatment has paralleled the advances that specific therapy has made. In spite of this, however, the authors feel that desensitization, though an accepted principle, needs to be improved. This form of therapy must be simple, safe and lasting. This might be accomplished finally by such procedures as slowly absorbing antigens, by modified antigens or by separation of haptenic from complete antigens. There are many puzzles that require solution to help perfect our knowledge and practice of allergy.

Schick[81] further points out that no immunity exists in serum sickness. He explains that the statement, "Allergy does not lead to immunity," is correct when relating to allergy and serum sickness and in all diseases of a similar nature. The lack of such immunity in allergic diseases consitutes a pathologic form of allergy. In endotoxic diseases such as smallpox, allergy here establishes immunity. This is an example of the physiologic or beneficial form of allergy which is needed for sustaining health. He reminds us that the inhibition of an antigen-antibody reaction can be a double-edged sword. The inhibition may be desirable because it might be considered advisable to stop an undesired reaction. On the other hand, it could be disadvantageous or even dangerous to inhibit other antigen-antibody reactions which are beneficial and necessary for our fight against infective germs. He reminds us that physiologic allergy is life-saving and outweighs by far the disadvantageous symptoms seen in cases of pathologic allergy of which anaphylaxis is its most intensive effect. Sevag[84] has stated that the allergic phenomena are characterized by abnormal responses to physical and chemical stimuli. These abnormal responses are anaphylaxis, hay fever, asthma, itching, vesiculation and other evidences of response. The allergic types are differentiated from each other by their peculiarities. For example, atopic allergy is characterized by the predominance of an hereditary tendency which is absent in the anaphylactic or serum sickness type of sensitivities. Bacterial type of allergy is further differentiated by delayed inflammatory skin reaction, by absence of blood-borne antibody and by the difference of sensitivity induction. Hypersensitivity as a common denominator, however, underlies all allergic phenomena. He views antibody, reagin and the like as

abnormal or potentially toxic products resulting from the actions of foreign agents on host metabolic systems. He has shown that enzyme-protein in cells, while being labile, are most vulnerable to the action of foreign agents with simple chemical structure. These agents can influence cellular proteins and induce the emergence of hypersensitive mechanisms in the cells. Tissue cells acted upon by foreign agents are induced in some manner to part with certain normal activities and accept less favorable alteration as a way out for survival. The hypersensitive mechanism acquired in this manner can be looked upon as an adapted process to escape destruction.

Aikawa[4] planned to hyperimmunize rabbits initially by the repeated intravenous injection of large doses of horse serum and subsequently to challenge them with small doses of antigen administered parenterally. He attempted to correlate the alterations in serum sodium and potassium concentrations and antibody nitrogen titer with the immunologic findings. The experiment utilized six domestic rabbits, observed over a period of 211 days. There was a definite decrease in the serum sodium concentration and an increase in the value for Na^{24} as related to body weight. Cortisone appeared to suppress both the antibody response and the abnormal physiologic responses. The most consistent finding in this study was a reduction in body weight during the period of sensitization. The simplest explanation for this would be a reduced intake of food and water. The transient increase in the serum sodium was due to dehydration. However, weight loss again occurred when the sensitized animals subsequently were again exposed repeatedly to this specific antigen. The water content was increased in most of the tissues examined.

Food and Drug Administration.—A primary health requirement in cosmetics is that these substances not be dangerous to the users. The frequency of reactions seen among users of cosmetics makes it essential for all of us to learn as much as we can with respect to the offending ingredient. Kerlan[45] reports that the principal responsibility of the Food and Drug Administration is to provide consumer protection through enforcement of federal legislation. This insures foods, drugs, devices and cosmetics to be wholesome and unadulterated, safe to use, sanitary in their preparation, and supplied with honest and informative labeling. If foods carry no definition nor standard of identity, the label must show the common or usual names of each ingredient. If there are two or more ingredients in the container, the substance may be designated generically without naming each component. However, spices, flavoring and coloring must be identified. Because of the nature and frequency of problems in the drug field, The American Academy of Allergy and The American College of Allergists have set up a joint committee to co-operate with the Food and Drug Administration.

Diagnosis of Allergy.—It is recognized that the diagnosis of allergic disease is often confusing and difficult. Steele[88] has analyzed the allergy records of a general hospital. Because of the laxity with which a diagnosis of allergy was made, he has devised a system by which the diagnosis of allergy is based upon a "point scoring system." Various points are assigned to each factor, based upon the following: a characteristic symptom, a credible history, a positive family history of allergy, therapeutic response, blood eosinophilia in excess of 4 per cent, positive scratch or

intradermal tests, and the demonstration of circulating antibodies by passive transfer reaction. A perfect score of fifteen points is practically unobtainable, but Steele believes that a minimum of four points is essential for a definite diagnosis of the allergic state. He has assigned one point or two points to the above factors with three points being allocated to the demonstration of circulating antibodies. He also emphasizes that certain organ systems seem more vulnerable than others to hypersensitivity reaction. Certain symptoms involving these organs are highly characteristic of the allergic reactions. He discusses these in good detail. The clinical and hospital charts of 234 cases which had been diagnosed as allergic disease were reviewed. Based upon his point scoring system, it was determined that slightly in excess of 20 per cent of these reviewed cases were diagnosed as "allergy" based on evidence less than Steele's minimum requirements.

Extract Fractionations.—Silver and Bookman[85] have fractionated four selected antigens—cattle dander, horse dander, ambrosia psilostachya (western ragweed) and Cynodon dactylon (Bermuda grass)—and have attempted to relate these fractions to clinical sensitivity. By ultracentrifuge and electrophoresis on filter paper they have studied the composition and uniformity of these extracts. The color of the cow and horse dander extracts seemed to be related to protein components, in that after precipitation the supernate became clear. This color intensity enabled the authors to follow the progress of migration on the filter paper strips in electrophoretic studies. They also found that analysis of the nitrogen content of the precipitated epidermal antigens was about three times that of the raw unprecipitated material when compared on a basis of original weight. On skin testing the fractions of the pollen extracts, it was found that no electrophoretic component was clearly implicated as a location of major antigenicity. Two or more strip segments showed skin test activity. Their studies seem to support the validity of using crude pollen extracts clinically, since our present knowledge is limited as to the composition of pollen extracts. The epidermal antigens were fractionated by the ultracentrifuge, but the low molecular weight of the pollen antigen (less than 10,000) did not permit fractionation by this method. The epidermal extracts showed fewer components by electrophoretic separation than did the pollen extracts. A previous review article by Halpin[40] has emphasized some of the reports related to the above discussion.

CLINICAL ALLERGY

Prevention and Prediction.—Early recognition and proper management of allergic disease in infants and children are big factors in the modification or prevention of major allergic disease in later life. The neglect of allergic problems in infancy and childhood leads to allergic cripples who cannot lead normal lives. Clein[16] emphasizes the presence of a definite chronologic order in the development of these allergic syndromes. The infant who has eczema may later have allergic colds and coughs, then hay fever and asthma or any other allergic symptom. Clein is in favor of adequate prophylactic measures being instituted early in life. The presence of allergy in early infancy can usually be recognized within the first few months. About 82 per cent of cases are diagnosed by four months of age and 90 per cent by one year of age. All of these infants are predisposed to major allergy, such as hay fever or asthma, in later

years. Clein has determined that one of every three infants with allergy has pylorospasm, persistent vomiting, or spitting up, with about one-fourth of the babies having gastrointestinal distress with colic, gas, diarrhea or constipation. Cows' milk allergy in infants is a classic example of the many slight-to-severe, ordinary-to-bizarre, common-or-baffling symptom-complexes. In his study of 206 infants with clinically proved allergy to cows' milk, twelve different clinical syndromes were observed. The symptoms of milk allergy usually appear between the ages of two weeks to two months, with 80% of these babies being able to tolerate milk after about four months. This author discusses in good detail each of the major allergic diseases affecting children. He emphasizes that allergic children should not have their tonsils and adenoids removed to correct the symptoms of the allergic cold, hay fever, or cough. Untreated allergic individuals have a tendency toward lymphoid hyperplasia. Clein believes that a simple, straightforward discussion of a child's allergic illness is part of the positive plan of treatment. The parents should be assured that the child will improve upon proper management. He has stated that the breast fed infant will avoid most allergic problems. The baby should never to be taken off the breast for a suspected allergic rash, pylorospasm or colic. All other means of avoiding possible allergens in the mother's diet or the infant's environment should be attempted before a change in dietary management is undertaken.

Active and immediate measures for prevention or control of allergic symptoms are of great importance. Prevention of allergy is as important as the active treatment of correction of the disease. Clein has found that change of climate is unnecessary in most instances of childhood allergy and that successful treatment may be accomplished by a thorough study and specific treatment of underlying allergic factors. He has stated that emotional or psychosomatic factors do not cause allergic diseases, but these factors may definitely aggravate existing allergic symptoms in the same manner as heat, cold, wind or friction. Ratner, Crawford and Flynn[74] believe that the ideal control of allergic disease should begin in the newborn period. Hereditary factors, according to these authors, do not influence the age of onset of allergic disease, since familial incidence is no greater in allergic infants than in allergic adults. As age progresses, sensitivity to foods decreases and that to pollens increases. During all stages of infancy the incidence of reaction to miscellaneous inhalants is relatively high while that of mold sensitivity is quite slight. It is interesting to note that about one-fourth of allergic infants react to milk constituents. The whey fraction is much more commonly incriminated than is the casein element. These authors have found that grass pollen is never the sole sensitizer, although tree pollen alone may be responsible for symptoms.

Emotional Behavior.—Harris and Shure[41] have sought, and reported upon, an objective method of evaluation to determine the presence of an underlying pattern of emotional behavior in bronchial asthma. These authors studied a large group of school children with the evaluation of the psychosomatic factors being based on an unbiased appraisal of the emotional problems and behavior pattern of each child as recorded by the teacher. These school children were between the ages of six and twelve years. They were well cared for, from excellent homes and with intelligent parents. The study included children from two elementary schools with a combined census of 1,489. The authors studied 1,263

children with twenty-five cases of asthma (constituting 2 per cent). They have tabulated the reports on these twenty-five children with asthma and have described the behavior patterns. In their control group of twenty-five children the same variety of deviations from the behavior pattern was noted. There is almost exactly the same number of shy children as of aggressive children, of obedient as of disobedient, of immature as of mature. The description of behavior is repeated in the asthmatic group and the control group in almost the identical number of times. There was no specific pattern discernible in either group. The study of these authors would indicate that although emotional disturbances are common, they are not limited or specific in asthma. The authors believe that emotional factors are often integral, though not necessary, parts of asthma.

It has been stated that children with allergy are likely to be found in homes of intelligent, somewhat neurotic, oversensitive and overanxious parents. Alvarez[5] has pointed out that during World War II thousands of neurotic and worrisome Jewish people were herded into concentration camps. During this time they seemed to forget their sniffles, asthma, arthritis, ulcers and mucous colics. In migraine, for example, Alvarez believes that three etiologic factors are usually involved; namely, the hereditary set-up, an element (often psychic) which sensitizes the person and sets the trigger, and finally the trigger—perhaps a cup of chocolate or a shopping trip. Though this author seems to believe that allergic sensitivity is one of several hypersensitivities, he does not, in the opinion of this reviewer, arrive at any definite decision in answer to his question: "Is allergy a psychosomatic disease?."

Abramson[2] believes that psychotherapy in allergic diseases may be either automatic or planned and purposeful. The automatic psychotherapy is that which is in evidence when the physician takes the history or recommends some form of therapy in outlining the procedures to be followed. The patient's symptoms, no matter how trivial or how serious, become a part of the doctor's life. This is an important process which led the patient, in the first place, to share his needs with the doctor and the physician's assistants. Planned psychotherapy consists of reassurance in explaining to the patient that his difficulty in breathing is only (?) asthma and that there is little or no danger of death. The administration of supportive psychotherapy is the understanding that the physician has for the patient's problems and the explanation that allergies are not a disease but a condition, and that the hives are in all likelihood a transitory phenomenon. The second type of planned psychotherapy, according to Abramson, depends to a greater extent on the personality of the physician, his medical education and his interest in psychotherapy. The physician sympathetically explores in more detail the personal and family relationships of his patient, his position in the community and his relationships with his work and hobbies. The large majority of patients will fall into these groups. It is the duty of the allergist to understand and to implement as much of the above-mentioned psychotherapy as is possible.

Bacterial Sensitivity.—Available to the clinical immunologist are suspensions of washed, killed, whole or ground organisms free of culture filtrate; solutions of formal and treated culture filtrate free of organisms; and combinations and materials derived from both organisms and filtrates. The work of Dworetzky, Baldwin and Smart[24] is concerned with the study of certain biologic activities of a cellular extract as compared with

a cell-free culture filtrate of pathogenic staphylococcus. From a staphylococcal infection of body tissue, the derived material is made up of intracellular and extracellular toxic and nontoxic proteins. Their culture filtrate was found to be deadly for intact rabbits and guinea pigs, whereas bacterial extract was not. Hemolytic and dermonecrotoxic activity was also found in the culture filtrate but not in bacterial extract. They summarize that their findings should serve to emphasize the importance of proteins, toxic or not, which are present within the staphylococcus. These proteins may play an important role in infection and hypersensitivity associated with this organism.

Szanton, Cohen and Rapaport[93] have reported their suggestive but not conclusive findings on the prophylaxis or bacterial allergy with repository penicillin in conjunction with hyposensitization therapy. This report covered a discussion of seventeen cases with controls. A clinical diagnosis of bacterial asthma had been made in all seventeen patients. The thirteen control patients were in the same clinical category of asthma with etiology established as bacterial allergy. Each patient in the group under treatment was given 1,200,00 units of a repository type of penicillin intramuscularly at four-week intervals. Treatment was continued for a period of five months between December, 1953, and April, 1954. All of these patients, in both the study and control groups, received their usual weekly hyposensitization injections; but the control group did not receive any repository penicillin. The seventeen patients comprising the treatment group provided the following results. Nine were improved as evidenced by decreased incidence of both asthmatic and respiratory attacks; five showed decreased incidence of asthmatic attacks only. In contrast, the thirteen control cases presented only two with improvement evidenced by a decreased incidence of asthmatic attacks alone.

The idea that infection is important in rheumatoid arthritis is a persistent one. Swineford, Coleman and Hyde[91] performed three sets of tests, using a wide variety of bacterial and other antigens, in a series of patients with rheumatoid arthritis. Over 4,000 skin tests were done. Their testing materials included, first, several mixtures of bacterial vaccines and nonbacterial antigens; second, mixtures of polysaccharide and nucleoprotein fractions of certain microorganisms; and, third, mixtures of seventy-two-hour-old broth culture filtrates of microorganisms. The results of skin tests with the vaccines and with the allergens showed no preponderance of reactions to Cecil's strain of arthrotropic vaccine. A total of 2,164 skin tests were done with this material, with 38 per cent of these tests resulting in a positive reaction of the immediate type and 45 per cent in the delayed type. Of the 917 skin tests done with crude polysaccharide and nucleoprotein fractions, the incidence of immediate and delayed reactions of all intensities was less than with the above-mentioned vaccine. There was no real preponderance of reactions to any one antigen. Skin reactions in 1,035 instances to mixtures of filtrates showed no preponderance of reactions to any one species of organisms. Sixty-four patients were treated with injections of an arbitrary mixture of the antigen; and, of these, only eight showed unequivocal improvement.

The immediate anaphylactic and delayed infectious states are not disposed to appear under the same circumstances of antigenic stimulation despite the fact that they can both be responses to the same antigen. Raffel[72] has found that when tubercle bacilli had been deprived of lipids extractable by chloroform they simultaneously lost the ability to induce

bacterial hypersensitivity. The protein antigenicity of the treated bacillary bodies remained virtually intact. By re-adding extracted constitutents to these defatted bodies, it was established that a fatty substance was essential for the sensitizing process. The activity of this substance was of non-antigenic character. The presence of this substance in the tissues simultaneously with antigenic proteins of the organism causes the animal to develop a bacterial type of hypersensitivity. It is believed that plasma cells must be involved in antibody production and that lymphocytes also in some fashion must be concerned in the process. Since hypersensitive subjects respond locally as well as systemically to antigen in the absence of circulating antibodies, it has been suggested that widespread reactivity of cells is characteristic of bacterial hypersensitivity.

C-Reactive Protein.—C-reactive protein (CRP) is found in the blood within a few hours after the onset of certain infections and conditions producing tissue damage. The sensitivity of this test as an index of disease seems to be of about the same order as the sedimentation rate for red blood cells. It has the advantage, however, of not being influenced by such a factor as anemia. Smith and Skaggs[98] explain that the name C-reactive protein comes from the fact that it reacts with a carbohydrate of the pneumococcus to form a precipitate. The CRP test may be one more screening device in allergic conditions and other chronic diseases in which the exacerbations are likely to mask the appearance of acute disease. This may hold true, however, provided the test is not affected by the allergic disease. They measured the C-reactive protein in 100 patients with bronchial asthma in whom infection seemed to play the sole or major role. In all but a few of these 100 patients, there were no positive skin reactions to a large number of test allergens. Of these 100 asthmatic patients, seventy-nine had no CRP in their blood stream. Seven had a 1+ reaction, and fourteen had 2+ or more. There were no infectious nor neoplastic diseases recognized in these seventy-nine patients with negative CRP tests. Positive CRP reactions appear to be related to the presence of other diseases rather than to the severity of bronchial asthma. They consider the C-reactive protein response to be of double interest for the allergist, primarily as to its clinical usefulness as a test, and secondly as to its meaning in immunology. They could find no relationship between the allergic symptoms and the presence of C-reactive protein in the blood stream except in the occasional case of urticaria. Twenty-two patients with infected asthma were given typhoid vaccine and most of these gave a CRP response.

CRP tests were performed on 109 asthmatic patients manifesting 222 diagnostic situations by Tuft and Scherr.[99] They could find no correlation between the sedimentation rate and the CRP reaction, particularly in the febrile group manifesting positive CRP reactions. Most positive CRP reactions were noted in active rheumatoid arthritis and active rheumatic fever. They were unable to confirm the suggested role of the CRP test in the etiologic diagnosis of bronchial asthma. In their group of 109 patients they found sixty-nine positive CRP tests, for an over-all ratio of 31.1 per cent. The highest percentage of positive reactions occurred in the group of febrile quiescent patients. These authors were unable to bear out the conclusion advanced by previous investigators with reference to the role of CRP in the diagnosis of allergic diseases.

The investigations of Libretti and Kaplan[54] clearly indicate that a

consistent positive relationship does exist between the early production of CRP at the time of the contact of the antigen with the host and the subsequent production of a high titer of antibody. They believe that there is a rough quantitative correlation between the amounts of CRP appearing in the serum and the response to a streptococcal infection with a subsequent rise in antibody titer. Their studies would indicate this additional evidence supports the contention that immunologic evidence of antecedent streptococcal infection may be found in every new attack of rheumatic fever. The highest antibody titers were noted within three weeks of the onset of acute rheumatic fever. The appearance of varying amounts of CRP in the serum was found to be concomitant to a relative decrease of the antibody titer during the so-called "acute phase response."

Polio.—It has been recognized that the number of cases of poliomyelitis will follow closely the height of the pollen seasons. Leary, Hodge and Schwartz[92] show that the peak of poliomyelitis incidence parallels and follows the height of both the grass and ragweed pollen seasons. Their patients, who had had poliomyelitis, reacted about twice as often to pollen as might be expected in a random sampling of the general population. They demonstrate graphically their conclusion that the increase in poliomyelitis during a period of six years was seasonal. It was always preceded by the peak ragweed pollen count by twenty-three to thirty-four days earlier. The time interval was repeated year after year with great fidelity. For four consecutive years the pollination of grasses preceded the large early peaks in poliomyelitis cases. Of their fifty patients, ten had a history of grass or weed pollinosis; and all of these gave positive skin tests to pollen. Eight of the patients had a family history of grass or weed pollinosis. They believe that the possible relationship between poliomyelitis and pollinosis may be purely fortuitous.

Polio Vaccine.—Poliomyelitis vaccine is prepared by growing representative strains of the three known immunologic types of poliomyelitis virus in tissue cultures. Bierly[11] believes that allergists and immunologists should be interested in learning in some detail about the ingredients and the methods of preparation of poliomyelitis vaccine. Using carefully cleaned and sterilized glassware, a specified amount of trypsinized fresh monkey kidney cells is added to Povitsky bottles containing a synthetic medium and .5 per cent horse serum. The presence of animal serum is necessary to "start" the cultures. The synthetic medium is a mixture of amino acids, salts, vitamins, minerals and an indicator such as phenol red. This mixture of kidney cells and antibiotic-containing medium is incubated for approximately seven days. The antibiotic—penicillin G, neomycin and dihydrostreptomycin—is added prior to the incubation to bring the final concentrations to 200 units, 0.1 mg and 0.2 mg per cc. respectively. The medium is then washed prior to the addition of the poliomyelitis virus. The series of washings and the restoration of volume not only reduced the horse serum content to less than one part in 5,000,000, but these procedures also reduce the antibiotic concentrations to minute amounts. The penicillin content, therefore, is reduced by washing and redilution alone to approximately .003 unit per cc; the neomycin content to approximately .0000015 mg per cc; and the dihydrostreptomycin content to approximately .000003 mg per cc. In recent months, poliomyelitis vaccine has been prepared with the addition of polymixin B and

dihydrostreptomycin in preference to the penicillin addition. Bierly lists the essential ingredients of poliomyelitis vaccine to be medium 199 (above described); horse serum in a final concentration of less than one part in 5,000,000; phenolsulfonephthalein .002 per cent; soluble monkey protein derived from blood or kidney; antibiotics; formaldehyde 1-4,000; preservatives; and poliomyelitis virus protein and nucleoprotein. *It is very unlikely that persons sensitive to horse serum will react following administration of 1/5,000,000 cc, the calculated amount of horse serum contained in 1 cc dose of poliomyelitis vaccine.* This amount of horse serum is so minute that the federal authorities do not require a label statement concerning the fact that horse serum has been added during processing. The preservatives and antibiotics added after washing and redilution must be declared, however. It is the general belief that *the number of individuals who are so extremely allergic to penicillin that they would manifest either immediate or delayed reactions to such small doses of penicillin as are found in this poliomyelitis vaccine must be few indeed.* Bierly could find only two reactions which could be considered as allergic when the vaccine was given to 939 individuals receiving a total of 2,350 injections. Both of these reactions were generalized nonurticarial rashes appearing on the fourth to the sixth day following the injection of the first dose and disappearing in twenty-four hours. He has suggested that only continued, widespread use of poliomyelitis vaccine will determine the potential antigenicity of this vaccine with regard to both primary sensitization and the causation of reactions in those already hypersensitive to one or more of these ingredients.

Multiple Sclerosis.—Before allergy can be incriminated as a cause of multiple sclerosis, certain criteria must be fulfilled. Historically, these criteria have been indicated to be an allergic constitution, a repetitive history of symptoms, a history of excessive contact with the allergen and positive skin test reactions. Prigal [67] believes that the elimination of a suspected allergen, if extrinsic, should relieve the symptoms and that deliberate reintroduction of the suspected antigen should reproduce them. This may not be true, however in a disease entity in which allergy is not the sole factor but is associated with one or more agents acting simultaneously. In this instance, the allergen is intrinsic and cannot be eradicated. This author has encountered only one patient with multiple sclerosis who has had hay fever. One of the chief characteristics of multiple sclerosis is the periodicity of the exacerbations and the remissions. Skin testing has not been correlated with multiple sclerosis nor has a history of unusually excessive contact with an allergen been substantiated by previous investigators. Prigal shows, however, that despite this negative evidence there is a basis for considering allergy as a mechanism for the induction of multiple sclerosis. The strongest evidence for this comes from investigators who are immunologists and who, under controlled conditions, have shown clinical and pathologic pictures resembling multiple sclerosis. The possibility is strongly suggested that though sensitization to nervous tissue has been produced in the experimental animal this does not necessarily indicate that the same may be achieved in man. Hypersensitivity to nervous tissue has been intimately associated with myelin in the demyelinative process. The relevant allergen, if accurately determined, would be of an extrinsic nature except perhaps the ingestion of nervous tissue in the form of food. On occasion, infection has been suggested as a factor in

the liberation of an antigen from nervous tissue which produces autosensitivity. It has been recognized by this author and other investigators that the pathology of multiple sclerosis is compatible with underlying allergic mechanisms. Prigal concludes that the demyelination processes can be induced on an allergic basis, but this should be considered as nonatopic and probably as a form of autosensitivity.

Mucous Membrane and Contact.—Acrylic plastic materials have been used as substitutes for vulcan or rubber in the preparation of artificial dentures for the past several years. During this time there has been a noticeable increase in the frequency of irritation or inflammation of the oral mucosa resulting from the use of such plastic dentures. Tuft and Santor[100] have reported a patient with stomatitis in whom they were able to obtain definite proof of an allergy to the acrylic plastic materials. The specific diagnosis was made by the clinical history of symptoms after repeated attempts to wear the plastic denture. Complete relief was experienced when the denture was removed. Their patient had a positive pressure test with the denture. Allergic sensitization to chemical agents like acrylic resin usually is acquired by contact. They present the possibility that this patient possessed a natural allergy to plastics inasmuch as she was unable to use a plastic pillowcase without symptoms of nasal allergy. Their patient also was sensitive to morphine. The positive patch test reaction to the liquid monomer (methyl methacrylate) is emphasized as the accurate method of establishing the accurate diagnosis of such contact.

Fungus Sensitivity.—The true etiology of a cutaneous sensitization arising from a present or past infection with a fungus of the genus trichophyton can be demonstrated by an intracutaneous test with an appropriate extract. The reaction is usually that of a delayed type, but Cohen[17] has reported the presence of an immediate wheal-type urticarial response. His patient, showing an immediate wheal reaction to trichophyton extract but with a negative delayed response, was not an atopic individual. Cohen does not believe that the immediate reaction was a false positive one since the same reaction occurred with trichophyton extracts of three different sources. He was able to culture *Trichophyton gypseum* from the crural lesions. Intracutaneous testing with Trichophyton extracts resulted in the immediate positive wheal flare response. The author was unable to demonstrate or prove the presence of circulating reagins to trichophyton.

Ocular Changes.—Organic ocular changes may be produced by psychic and allergic trauma. In susceptible individuals these may be just as profound as those produced by direct physical trauma, extreme anoxia, altered metabolism, infection or other pathologic pictures. Prewitt[64] believes that psychosomatic and allergic factors should be given high priority whenever one seeks to determine the cause of ophthalmologic disease. Allergy and stress produce an excessive parasympathetic stimulation or parasympathotonia resulting in a smooth muscle spasm of the arterioles and venules. Capillary dilatation will result with stickiness of the vessel wall, increased premeability, transudates, edema, anoxia and finally obliterative arteritis. This pathologic picture will result from either psychosomatic, allergic or traumatic backgrounds. Prewitt suggests that there should be a careful balance among avoidance of causative

agents, desensitization, counteracting infection and symptomatic medication. Therapy should be directed toward the effort to remove the psychogenesis. He follows the course that the physician should not sensitize the patient to emotions by the questions that are asked and by the implications that are left.

Blood Protein.—Agammaglobulinemia not infrequently follows an infection in early childhood. The condition is much less common in adults. The presence of agammaglobulinemia in a fifty-three-year-old woman has been reported by Wechsler and Wolf.[106] In this instance the original diagnosis of agammaglobulinemia had been made at the age of forty-seven. She had spent her entire life in the city. The defect in gamma globulin synthesis in this woman was an acquired one. The patient had shown numerous recurrent infectious processes over a period of the several months prior to the institution of gamma globulin administration. Except for minor upper respiratory infections not associated with fever and for which she was given short courses of antibiotic therapy, the patient remained well with the administration of gamma globulin by injection.

Mucoviscidosis.—The first sign of cystic fibrosis of the pancreas in a newborn infant is likely to be meconium ilius. The mucoprotein is undigested because of pancreatic stoppage; and with the accumulation in the bowel, acute intestinal obstruction is produced. This usually leads to surgical intervention. Later the patient has a hearty appetite but fails to gain weight. Growth is retarded, the abdomen is distended and rectal prolapse may occur. Cystic fibrosis of the pancreas is of interest to the allergist because the patient, sometime before the age of six, may develop a mild cough which progresses into wheezing, hoarseness, recurrent respiratory infection and such pulmonary complications as emphysema and bronchial obstruction. The organism usually found during any infection is *Staphylococcus aureus.* This report[7] reveals that duodenal intubation with assay of the pancreatic fluid for enzymes is of considerable importance in establishing the diagnosis of fibrocystic disease. In the absence of enzymes or with a very low titer of trypsin, the diagnosis can be confirmed. It is important, also, to measure the activity of other pancreatic enzymes. The control of pulmonary infection constitutes the most important aspect of the management of this disorder. Broad spectrum antibiotics are extremely useful. Despite improvement in the management of these patients, the prognosis remains poor. The majority of the patients with this disease die before the age of five years because of progressive destruction of the lungs. Many of these children will be seen by the allergists with a referred diagnosis of bronchial asthma.

"Anaphylactic Sets."—Severe anaphylactic reactions may occur following the administration of drugs, serum, antigens, antibiotics and local anesthetics. They may also follow the sting of a wasp, bee or yellow jacket. The physician is usually unprepared to cope with such reactions because of the suddenness and unexpectedness with which they occur. To combat this lack of preparedness Prickman and Lofgren[66] have prepared a so-called "anaphylactic set" which they have placed at strategic points in their office and hospital. They believe that all of the necessary emergency drugs and the equipment for their administration should be readily

available. Their anaphylactic sets contain the following items: two 1 cc ampules of 1-1,000 epinephrine, two 2 cc syringes, two hypodermic needles, two long needles (one inch and four inches long), two ampules of aminophyllin 3¾ grains each, one 1,000 cc bottle of 5 per cent solution of dextrose in distilled water, one intravenous set, one 10 cc ampule of Benadryl,® one bottle of hydrocortisone (which, diluted to 2 cc, gives 50 mg per cc), one ampule of sterile water, one scalpel, one hemostat, one ampule of absorbable cat gut with needle, alcohol, gauze sponges, swab, tongue blade, and one 20 cc syringe. These authors also recommend that an oxygen tank and mask might be considered important and should be readily available. It is their impression that the majority of anaphylactic reactions can be properly administered with the above preparations. The anaphylactic reaction from any source should be considered as an emergency from which the patient may readily die.

Education in Allergy.—The attention of the reader is directed to the reports of the survey made by the American Foundation for Allergic Diseases on the subject of undergraduate and graduate education in the field of allergy.[8,21,46,49] The survey of undergraduate education reveals that more than one-third of the medical schools do not present courses in allergic diseases. Only twelve of the seventy medical colleges have been approved for residencies and fellowships in allergy by the American Board for Medical Specialties. Thirty-one medical schools have no funds available for research in allergy. Thirty-four medical schools have increased instruction in allergy in the past five years, but thirty-three have not. All but five of the schools have allergy clinics, and fifty-nine of the seventy use the clinics for teaching purposes. Certification in allergy predicates not only the existence of standards for the training of allergists but also the existence of teaching programs in recognized and approved training centers. There has been a significant evidence of progress indicated by an increase in total number of residencies and fellowships in allergy in 1955 as compared to 1949. There has also been an increase in approved residencies and fellowships, an increase in the institutions with allergy programs and an increase in the institutions with approved programs. The development of teaching facilities for the training of allergists has been traced with the impression that the properly trained internist or pediatrician must have some knowledge of the clinical manifestations of allergy, its recognition and the management of these patients. Allergy training should be required as part of the residency training for internists and pediatricians.

Allergic Shock (?).—Laub[51] has reported an interesting case in which allergic or anaphylactic shock was due to the use of cosmetics. Repetition of the shock while the patient was hospitalized was noted at the merest smell of perfume or the touch of the nurse's fingers which had face cream on them. In these latter instances, the author considered these to be psychogenic shock. The original onset of the patient's symptoms of shock was noted after the application of a face cream containing orris root, to which the patient was sensitive. The case was reported by Laub because the symptoms occurred with such rapidity and with such severity that attention should be drawn to the acute shock which may result (?) from cosmetic application.

RESPIRATORY

Asthma Recurrences.—A patient is not unreasonable in his desire to have his asthma relieved to the point where he is completely comfortable. Prickman[65] proposes that asthma is the result of inflammation of the lower part of the respiratory tract. Evidence is found on both gross and microscopic examination of sections of bronchi of patients who have had asthma. Cellular infiltration, thickened basement membranes, hypertrophic bronchial lining raised in folds are the conditions that are usually seen microscopically. All of these findings constitute evidence of the presence of inflammatory disease. Most persons with asthma admit that the recurrence of bronchial asthma is discouraging. The usual cause of a recurrence may be a respiratory irritant such as a neglected infectious head or chest cold which came on when the patient was tired and run-down. For this reason, Prickman emphasizes that the patient should regard a first, mild cough with attention and respect because it may be the warning signal of asthmatic recurrence. The cough also warns the patient to avoid something that may be noxious to him or to deny it excess. Such things are smoke, other fumes, dust, allergens and frosty air. Less concrete influences may be sudden changes in temperature, circumstances that induce coryza, exertion and hearty laughter. The principles of treatment of inflammation of the air passages are no different from those of treatment of inflammation of any other diseased tissue. Healing will begin only when the cause of the inflammation has been removed. This author discusses the emergency measures that can be undertaken to relieve a patient of his asthmatic complaints. He emphasizes that complete recovery is impossible when emphysema complicates bronchial asthma. However, much relief may be anticipated from treatment designed to clear up all inflammation of the air passages so that the patient has only the damaged lung with which to contend. He advises the control of cough and bronchospasm, together with their causes, so that emphysema should not increase.

Rackemann[71] believes that mixed causes such as allergic, infectious and psychogenic are present together in almost every case of bronchial asthma. Physical stress such as cold, undue exertion or just plain fatigue can result in bronchial asthma. Psychogenic stress can cause asthma, but only in those patients who have the background for asthma. In offering relief for the acute attack, the physician must ask himself two questions. The first is: "What shall I do now to relieve the bronchial obstruction?." In answer to this the author discusses the use of epinephrine, xanthine preparations, nebulized solutions, corticosteroids and antibiotics. The second question which the physician must ask himself is: "What causes the asthma and what can I do to prevent further attacks?." The answer to this problem depends upon the history, the age of onset, the present age of the patient, the course of the disease. whether the symptoms appear in attacks or are persistentlv present and whether there is relation to changes in season or environment. In other words, the whole patient must be studied and treated. Rackemann recognizes that, while ACTH and cortisone are very useful, they cannot replace the more simple and less dangerous drugs which will relieve bronchial asthma. The real problem facing the allergist today is the background of bronchial asthma; namely, the reason why some individuals and not others are subject to attacks of bronchial distress.

Asthma and Emphysema.—The basic problem in emphysema is the obstruction to respiratory airflow in an individual with an inherently irritable bronchial tree. Feffer and Mann[28] state that the normal bronchi dilate during inspiration and contract during expiration. Bronchial obstruction will be exaggerated during expiration, tending to make complete expiration difficult. Patients with chronic emphysema are susceptible to recurrent attacks of acute bronchitis, bronchopneumonia and moderate bronchial obstruction. Infection will increase bronchial obstruction and diminish alveolar ventilation. This usually leads to acute anoxia and carbon dioxide retention. The rate of respiration and tidal exchange in emphysema is dependent upon the hypoxic stimulus. This stimulus is eliminated if oxygen or sedation is given. The administration of oxygen to the patient with emphysema should be accomplished only by nasal catheter, starting at the slow rate of one liter per minute and gradually increasing by one liter per day.

In answer to a question regarding the therapy of bronchial asthma which is complicating myocardial infarction[68] the use of corticotropin or the corticosteroids was stated to be definitely indicated to relieve the airway obstruction. This was particularly true if other therapy was found not to be immediately effective. The myocardial infarction was not a contraindication to the use of these preparations. The consultant stated that oxygen therapy was essential to a patient with bronchial asthma in an acute attack of myocardial infarction unless there was chronic diffuse obstructive emphysema of long standing and then the administration of oxygen should be given with extreme care. Krantz[50] states that the use of aminophyllin intravenously in status asthmaticus should be enjoined with special caution, as there have been so many misadventures in therapeutics with this important restorative measure. This reviewer agrees with this statement but adds that the proper administration of aminophyllin preparations in status asthmaticus will not be associated with many misadventures. Emphasis must be placed on the above words, "proper administration." The injection must be given slowly, with at least eight to ten minutes being required for the administration of 20 cc of solution (0.5 grams). It is difficult to obtain adequate dosage levels in the administration of aminophyllin orally without producing gastric irritation. This author suggests the use of the less irritating theophyllin sodium glycinate or the use of enteric-coated aminophyllin tablets. ACTH owes its value to its stimulating effect upon the adrenal cortex from which it induces the secretion of the adrenal steroids. The mechanism by which the corticosteroids promote relief in bronchial asthma is not clearly understood. The steroids serve to restore to normalcy diffusion through the capillary membranes. Tissue metabolism is also stimulated by the steroids and gluconeogenesis is produced through protein destruction. This action might involve the destruction of the protein portion of the allergotoxin molecule. Krantz adequately discusses the use of the well-known drugs for the relief of asthmatic symptoms. He believes that gamma globulin fraction in the treatment of asthma is a factor of definite promise. Although the serum fraction is very costly, it does appear to render certain asthmatic patients refractory to the disease for long periods of time in his experience. This is particularly true in small children. He points out that there is much room for improvement in the treatment of asthma, and that rational therapy is still in its incipiency.

Globulin.—Tuft[97] has reported on the results of serum electrolysis performed on asthmatic children who were admitted as intractable cases to the Jewish National Home for Asthmatic Children. Electrophoresis was performed by the paper technique. All of the 126 asthmatic children had severe perennial asthma and were subject to repeated respiratory infections followed by asthma. The most chronic asthmatic of these patients showed significant variations in all except the alpha and beta globulin; while, in those with less asthma, variations were significant in all fractions except beta globulin. In the group of patients whose last asthmatic attack had been more removed, the variations were noted only in albumin and gamma globulin. His findings would suggest that elevated gamma globulin alone is responsible for the evident reduction in the electrophoretic albumin-globulin ratio of a recovered asthmatic population. Tuft did not find any instances of agammaglobulinemia among his patients, despite the fact that the history of all of these children showed a distinct susceptibility to repeated respiratory infections. Because hypergammaglobulinemia was demonstrated in the group studied at least thirty-one days after their most recent attacks of asthma, it should be noted that increased amounts of gamma globulin accompany the recovery phase of asthma. Tuft postulates that such increases are necessary for recovery. This feature may provide a sound basis for injection of gamma globulin to susceptible individuals.

Controlled Evaluation.—The superiority of institutional evaluation of anti-asthmatic medication has been pointed out by Tuft and Kraus.[98] Their controls were paired, with one member of the pair receiving the medication and the other member receiving a similarly appearing but inactive substance. However, the selection of control groups in asthma with regards to severity of disease is recognized to be practically impossible. True evaluation of any drug for the relief of asthmatic symptoms cannot be accomplished in the relief of acute bronchial asthma. The chronic asthmatic cases constitute the only group in which such evaluation is possible. Environmental factors and psychogenic factors must also be considered in such evaluation.

Feinberg, Feinberg and Benaim-Pinto[30] report that many of their patients whose symptoms were not entirely explainable on any other etiologic basis did react on scratch test to insect antigens. Forty-four of 130 patients had seasonal symptoms only; but in eighteen of these forty-four, the mold and pollen reactions could not explain the particular season of the individual symptoms. Of the 130 patients reacting with insect antigens, the symptom pattern with seasonal aggravation or with perennial complaints aggravated during the summer months could not be explained solely by pollen and mold allergy in forty-five patients. In these instances, the presumptive evidence of clinical allergy to insects is quite strong.

Asthmatic patients were advised to stop smoking and to practice breathing exercises before undergoing surgery. Walton[103] advised that patients in severe bronchial asthma be operated under local or block anesthesia. If general anesthesia was used, ether intravenously or by inhalation was employed as the anesthetic of choice. Once good sleep was induced, the anesthesia was continued by inhalation ether or by nitrous oxide and oxygen. Anesthesia produced by intravenous-plus-inhalation ether can be controlled and is not dependent upon the rate or depth of respiration.

Ether is also suggested as the ideal anesthetic for an asthmatic patient because of the recognized beneficial effects which this preparation has upon the normal course of bronchial asthma.

The disease triad of chronic pulmonary infection, fibrosis and emphysema usually produces an exorable downhill course in most patients. Leslie and Rosove[53] have found the available therapeutic measures to be relatively ineffective in the past. They have been impressed with the beneficial results from intermittent positive pressure breathing combined with power nebulization of bronchodilator drugs. These authors studied thirty-three patients with moderate-to-advanced pulmonary emphysema associated with various degrees of bronchospasm, fibrosis, bronchiectasis and chronic bronchopulmonary infection. They desired to determine the immediate effects of various power nebulized bronchodilators administered alone and combined with intermittent positive pressure breathing. They wished to determine for each patient which bronchodilator was most effective. Neither the positive pressure breathing nor the bronchodilators alone are useful in conditions associated with bronchospasm. The improvement seen with the bronchodilators was not significantly enhanced by the intermittent positive pressure breathing. Over longer periods of time with and without the pressure breathing, the benefits did not appear to be enhanced by the breathing adjunctives as compared to the power nebulization of good bronchodilators.

Air Filtration.—Is there any scientific evidence for the claims that a room air-conditioner can effectively filtrate pollens? The answer to this question[69] stated that the effectiveness of most filters is purely relative. As a result of many tests, most filters will remove pollens from the air to a greater or lesser extent, but the precipitator type is the most efficient. The relief experienced by a patient who depends upon a mechanical filter for protection will be dependent entirely upon his degree of sensitivity for the pollens to which he is exposed. It was stated that patients with pollen asthma do not have as good a response as those who have only nasal symptoms. A volumetric sampler was employed by Rooks and Shapiro[77] to study the efficiency of mechanical filters and air-conditioners in the removal of airborne ragweed pollen and certain fungus spores from the atmosphere. The rate of air flow used in all air samples was 0.5 cubic foot per minute and 0.5 cubic yard of air was sampled in each instance. The sampling rate approximates the volume of air inspired by an adult during normal activity. These authors used four different locations, two of which were protected by commercial window-type filtering units which supplied only filtered air, and two by standard air-conditioning units manufactured by different companies. A total of approximately 100 air samples was taken by their volumetric sampler at these four widely separated locations. Their readings indicate that mechanical filters are available which by filtration will reduce the incidence of ragweed pollen indoors to a mean dosage of seven per cubic yards of air. At the two locations out of doors the count was approximately 200 per cubic yard of air. It was also found that the mechanical filters were effective in the removal of airborne ragweed pollen, but the removal of hormodendrum and alternaria spores was not nearly as effective. They advised that patients should not depend completely upon either mechanical filters or air-conditioning units for the control of airborne fungus spores in a home.

Anderson and Ogden[6] selected thirty patients with nasal allergy for the study of prednisolone topically in these conditions. They found that a good amount of improvement could be expected with the topical use of the hormone whether the solution was 0.1 per cent or 0.05 per cent strength. They were unable to determine any visible changes in nasal polyps during this local treatment. They could not expect well-formed fibrotic tissue to be "dissolved" by hydrocortisone.

Tocker[96] tested seventy-nine fall hay fever patients with separate solutions of rough marsh elder and ragweed. Twenty-eight persons reacted only to ragweed, while six patients reacted only to marsh elder. He believes that there is a common allergen present in ragweed and rough marsh elder and, at the same time, an allergen that is mutually exclusive. His patients showing reactions only to the marsh elder extract had more symptoms compared to those with only ragweed reactions or equal reactions to both antigens. Because of the higher antigenicity of the rough marsh elder extract, therapy with this material must be cautious. He lists the incidence of marsh elder sensitivity as another problem confronting the allergist in giving adequate ragweed therapy and relief to the patient sensitive to fall pollens.

Bronchiectasis.—Strang[90] has recorded the results of a follow-up study carried out during the year 1950 on a group of children with bronchiectasis. All of his patients were under the age of fifteen at the time of admission to the hospital when the diagnosis of bronchiectasis was established. Of these, 208 children were followed over a period of time extending from two years to fifteen years with an average follow-up in the survivors in 6.4 years. Since these children were referred by physicians to a thoracic surgical unit, it was natural that emphasis was on surgical management. One hundred and sixty-three of the patients were treated surgically, and forty-six were treated with conservative measures. Pneumonectomy was performed in forty-eight cases. Fourteen patients have been called cured in that they have been in excellent general health, free of chest symptoms and able to do work without loss of time or to lead a normal active school life. Eighteen patients were considered greatly improved, and five showed slight but quite definite improvement. Two patients showed no improvement of any value. Three children must be considered as being worse, in that they did not thrive at all since their surgical procedures. Seventeen of the pneumonectomies were performed in two stages with the upper lobe being removed at a later stage than the lower lobe. One hundred and twelve cases were treated by lobectomy from which there were ten postoperative deaths. Five additional patients died since their discharge from the hospital, with death occurring between two and ten years postoperatively. Thirty-four of the remaining ninety-seven patients were completely free of chest symptoms. Thirty-eight were greatly improved. Fourteen children were slightly improved with severe residual chest symptoms, except two in whom the pre-operative symptoms were mild. Eleven cases were not improved as a result of the lobectomies. Medical treatment was outlined for the children, consisting of postural drainage, teaching the children how to cough so sputum was produced but not swallowed, and instructions regarding expansion breathing training. This medical treatment was recommended in forty-six instances, with these patients being considered as three individual groups: namely those in whom the disease was considered too mild for surgery, those in whom

the condition was too severe for surgery, and those in whom operation was either refused by the parents or for some other reason was not completed. Ten patients with bronchiectasis too mild for surgery were all well in their follow-up studies. Of the twenty patients with bronchiectasis too severe for surgery, nine patients had died, all within five years of hospitalization. The disease was bilateral in each instance of the remaining eleven patients. Ten were known to have carried out postural coughing during a period of two to seven years. In eight of these, the symptoms were about the same with physical signs still being present and the general health of the patients being poor. It is Strang's impression that medical treatment plays a most important part in the preparation of bronchiectatic patients for operation; but, at its best, medical treatment is considered essentially a palliative measure. The results of operative treatment in children suffering from asthmatic attacks were disappointing. Not only do the asthmatic attacks persist, but the cough, feverish attacks and dyspnea are not improved, particularly after pneumonectomy; and the child may be rendered anoxic. The presence of sinusitis in association with bronchiectasis is, in Strang's opinion, purely secondary to the bronchiectasis. It plays a part in keeping the pulmonary infection alight. He suggests that prophylactic treatment might be most useful before the disease becomes irreversible, with the irreversibility depending upon the virulence of the infection, the resistance of the patient and the degree of bronchial obstruction.

Respiratory allergy rarely exists alone, in the opinion of Dintenfass.[23] He believes that allergic rhinitis and bronchial asthma may be purely allergic at the time of their onset but almost immediately become complicated by infection. Allergy is often involved in the epidemiology of the common cold. Sinus disease, in the opinion of this author, may be an important cause of bronchial asthma. In the treatment of respiratory infection, the primary aims are to provide adequate drainage and ventilation. The causative agent should be removed. He also suggests the complete avoidance of offending allergens as being a desirable part of the treatment. Conservative surgery, to remove a septal spur or correct a deviated nasal septum, may be warranted to provide good relief to these patients.

Abnormal physiologic reactions in the mucous membrane of an organically normal nose comprise about 75 per cent of all nasal diseases, in the opinion of Nash.[57] This mucous membrane reaction is usually a temporary one and is therefore considered reversible. In contrast to this, however, is organic disease of the nose which involves destruction or proliferation of the tissue resulting in anatomic changes which become irreversible. Surgery is often necessary to correct these organic conditions. Uncomplicated allergic rhinitis is considered as a hyperfunctional disease with polyps or hyperplasia converting the condition to organic or irreversible illness. In allergic disease the nasal mucous membrane is pale because of detention of intercapillary spaces, but the mucosa with all other hyperfunctioning conditions is red, due to the increased capillary filling.

Most persons living in an endemic area for coccidioidomycosis acquire the infection, although usually the symptoms and signs are unrecognized. After an incubation period of eight to twenty-eight days, the symptoms may appear and vary from slight infection of the upper respiratory tract to rather severe symptoms similar to pneumonia. The most common

symptom is cough, but this is usually nonproductive. O'Leary and Curry[59] have found that the disease becomes disseminated in about 10 per cent of the patients and produces residual lesions. Bronchiectasis or atelectasis may occur as a middle lobe syndrome due to adenopathy. The coccidioidin skin test is highly specific except when used undiluted or only slightly diluted. This coccidioidin is not antigenic, does not interfere with any serologic tests, and does not reactivate old quiescent lesions. The skin test becomes positive in one to four weeks after the infection has been present. Most patients with disseminated coccidioidomycosis do not react to the skin tests. The etiologic agent *Coccidioides immitis* occurs in two phases; the first phase is a saprophytic form which is found in nature and is characterized by mycelia hyphae and arthrospores, and the second phase is a parasitic form, occurring in man and animals, and is represented by spherules and endospores. Medical treatment has been found to be ineffective. Surgical resection is usually the treatment of choice for giant cavities, areas of secondary infection and other continued lesions.

Loeffler's Syndrome.—Patchy migratory infiltrations seen in serial chest roentgenograms are findings that are characteristic of Loeffler's syndrome. The patients of Epstein and Kligman[27] were hospitalized for pneumonitis with symptoms of cough, dyspnea, malaise, and elevated temperature. Each of their seven patients had received from two to six graded injections of 3-pentadecylcatechol in sesame oil for prophylaxis against poison ivy dermatitis. The above symptoms appeared eight to forty-eight hours after the last injection. The only consistent features of these patients were the findings of pneumonitis and an eosinophilia with maximum counts of eighty eosinophils for one hundred white blood cells. The authors state that the eosinophilia whether allergic or not is, according to the hypothesis they propose, an indispensable central element in the pathogenesis of the lung lesions. In their seven patients, the intensity of eosinophilia paralleled the degree of allergic sensitivity. There was no doubt in their minds that it was provoked by an allergic reaction taking place in the tissues. From their available clinical pathologic evidence, the authors try to reconstruct the pathogenesis of eosinophilic pneumonitis as follows: the initial event is an eosinophilia, often allergic but sometimes of other cause. They do not believe that every drug reaction should be condemned as being allergic, stating that the eosinophilia provoked by drugs may have nothing to do with an allergic reaction. Similarly, if eosinophilic penumonitis follows the administration of a drug, it is obligatory that the observer prove the allegation of allergy. When huge amounts of 10 per cent solution of 3-pentadecylcatechol in sesame oil (8 cc) were given in one week to nonsensitive persons, a moderate eosinophilia up to 15 per cent developed. Either the oil or the material in the oil may have been responsible for the eosinophilia. Normally, such an amount would be administered to sensitive persons over a period of months. Regardless of how the eosinophilia occurs, it would seem that the lungs, and less importantly other viscera, have a tendency to trap or filter out the eosinophils in some unknown way. This may be because the eosinophils have an affinity for structures with high histamine reserves, of which the lung is supposed to be one. The authors do not subscribe to the belief that there is a natural relationship between the syndrome of eosinophilic pneumonitis and polyarteritis nodosa.

Abram and Frankel[1] report four cases in which the examination of these asthmatic patients revealed pneumonitis of the middle lobe with some associated atelectasis of this middle lobe. The important factor in this particular disease is its early recognition and treatment. This early recognition eliminates the later complication of permanent atelectasis and bronchiectasis which may require surgical removal of this lung segment. It is necessary to relieve the bronchial edema and also the bronchiolar obstruction. Bronchoscopy and surgical intervention in these instances are not warranted.

DERMATOLOGIC

Effects of Sunlight.—Conservative or rational use of sunlight or its artificial substitutes is considered to be healthful to most individuals, but the current habit of exposure to intense or prolonged sunlight is definitely open to question. This is particularly true during the first days of the season, before the individual becomes acclimated to this amount of sunlight. There has been a notable seasonal incidence of temporary incapacitating sunburn and an increasing number of diseases caused or adversely affected by exposure to the sun's rays. Kesten[47] states that the erythema caused by the sun's rays is produced by strictly definite wave lengths of ultra-violet between 2800 and 3132A. This is the so-called sunburn range. Ninety to ninety-five per cent of this erythemal radiation is absorbed by the normal white skin. Thickening of the horny layer of the skin, subsequent to exposure, is thought to be the main mechanism by which accommodation to sunlight occurs. This horny layer absorbs light strongly in the ultra-violet zone. These flat, horny and granular layers of the epidermis reflect and scatter the light. Thus, the sun's rays are prevented to a large extent from reaching the easily-damaged deeper skin layers. The presence of perspiration also provides some protection against sunburn. This author states that allergic eruptions caused by sunlight are not uncommon. Intense inflammatory reactions may follow exposures that cause no perceptible reaction in normal skin. Urticaria, purpura and other lesions may appear after minimal exposure. The ingestion of various drugs will cause some photosensitivity. It is not unusual to have the skin sensitized to sunlight after repeated contact with certain plants or some essential oils found in perfumes and cosmetics. The precipitation or provocation of lupus erythematosus has been suggested by the history of severe sunburn preceding the appearance of lesions or the increase in severity of existing lesions after exposure to sunlight. About one-fourth of the patients with lupus erythematosus have been found photosensitive when exposed or tested to sunlight. According to Kesten, the ideal suntan preparation should be hypoallergenic, nonirritating, nontoxic, stable in sunshine, and afford protection to the skin from sunburn for as long as three or four hours after application. She also believes that it should be nonstaining and reasonable in cost.

Solar urticaria is unique in that it may be caused by the blue violet of visible light or by specific wave lengths within the ultra-violet range in different patients. Chronic solar dermatitis, farmers' or sailors' skin, is considered to be precancerous by Stegmaier.[89] Sunlight, in his opinion, is one of the main causes of cancer of the skin. This condition is recognized to be more common in southern than in northern latitudes. When urticaria is produced by the rays in the blue zone of visible light between 4000 to 5000 A, antihistaminic products may be used to reduce the

sensitivity. He states, too, that exposure to long ultra-violet rays, usually less than 3700A, may precipitate solar urticaria. The skin may be sensitized to ordinary sunlight exposure by such drugs as Thorazine,® barbiturates, sulfonamides and other drugs. It has long been recognized that coal tar and pitch products may produce kerotoses, skin cancers, and may be elements of photosensitivity. Para-aminobenzoic acid and its derivatives sensitize skin to sunlight. Some of the diseases that may be aggravated by exposure to the sun are lupus erythematosus, pelagra, porphyria, vitiligo, albinism and pityriasis rubra pilaris.

In general, Cabaniss[14] agrees with the authors just mentioned. He believes that the dermatitis evoked by sunlight in a sensitive person is nonspecific and papules, wheals, vesicles or plaques may appear. Phenergan® may photosensitize the skin after either the systemic or topical use of this antihistaminic preparation. In his opinion, prophylactic care is extremely important in treatment. Therapy should be aimed at avoiding the sunlight. A gradual desensitization program is outlined by exposure to minutely graduated amounts of light, with the added use of sun screens of either mechanical or chemical nature. He advises that many of the chemical sun screens used to prevent sunburn may, themselves, be photosensitizing agents.

Margolis, Butler and Fischer[55] observe that 25 per cent of all patients taking chlorpromazine developed increased sensitivity to the sunlight after mild exposure. They have studied fifty-six patients receiving chlorpromazine therapy, seven of whom developed dermatitis as a result of drug ingestion. In six of these cases the dermatitis cleared quickly with the discontinuation of the drug. One patient did not clear until twelve days after the appearance of his dermatitis, even though the chlorpromazine was discontinued. The appearance of drug eruptions in patients on chlorpromazine therapy does not require the permanent discontinuation of the drug, but it should be withdrawn until the lesions have cleared. Then a gradual and careful resumption of therapy may be attempted.

The rare individual who is thought to be "allergically hypersensitive" to a bar of soap is often shown to be sensitive to some ingredient other than the alkaline salts and the fatty acids. In these instances, it is thought that the patient is probably hypersensitive to a dye or a perfume in a soap. Blank[12] investigated the sensitizing potential of a bar of soap containing tetra-methyl-thiuram-disulfide. The antiseptic in this soap is the same chemical that is used by the rubber industry as an accelerator. To patients who had been shown to be allergic to this same chemical in rubber adhesives, this investigator applied the soap (Lifebuoy) to their skins. He also used an 8 per cent aqueous solution of the soap. His control was a soap which appeared to be identical but contained none of the antiseptic. On the six persons tested, no significant reactions were seen to the 8 per cent aqueous solution of the control soap. Five of the six patients were considered to be sufficientlv hypersensitive to the antiseptic that further testing was discontinued. In spite of this, Blank was unable to observe any patient in his routine procedures who had a dermatitis in which it could be proved that the lesions were due to an allergic hypersensitivity to this particular soap. It had been reported by the company that there was only one case of skin irritation observed to this particular soap in over two million bars that had been retailed.

Nickel Dermatitis.—Contact with nickel and chromates may result in a dermal delayed (tuberculin type) sensitivity which is productive of contact dermatitis. Epstein[26] has reported thirty-four cases of contact dermatitis with nickel sensitivity. In all of these patients, patch and intradermal tests with nickel sulfate were performed and observed for at least forty-eight hours or longer. The patch tests were done with a 10 per cent solution of nickel sulfate. The intradermal tests were done with serial dilutions of this same material. Neither concentration produced any reaction in numerous controls. The majority of patients gave reactions to both patch tests and intradermal tests. The intradermal tests were tuberculin-type papular reactions, but in some instances a vesiculopapular dermatitis developed on top of the reaction. In addition, 42 per cent of the tested patients gave a positive reaction to copper, which demonstrated the relationship between patch and intradermal tests in copper sensitivity resembling that in nickel sensitivity. Epstein studied eighteen cases with chromate sensitivity. Patch tests were performed with a 1 per cent aqueous solution and intradermal tests with 1:100,000 dilution of potassium dichromate. All but two of these chromate sensitive patients showed positive reactions to both patch and intradermal tests. In eight of these patients, patch and intradermal tests were done with nickel and copper; but no patient reacted to these metals.

Nickel contact dermatitis presents some clinical peculiarities. The dermatitis is usually a papular or papulo-vesicular dermatitis and is not a bullous contact dermatitis. Some of the lesions may resemble atopic dermatitis much more than they do the typical lesions of contact dermatitis. Intradermal testing, with suitable extracts, in cases of suspected contact dermatitis probably would reveal positive reactions and demonstrate specific sensitivity in a great number of cases. This is especially true to localized contact dermatitis where patch tests are negative. Such a procedure, however, cannot be recommended as practical because of the possibility of provoking sensitization. If dermal sensitivity plays as much of a part in contact dermatitis as Epstein believes, then desensitization in contact dermatitis may be reconsidered. He did not attempt to desensitize his nickel sensitive patients because elimination of the contact was simpler and safer.

Nickel was found to be the cause of dermatitis in 198 patients seen over a five-year period by Fisher and Shapiro.[33] Positive patch tests with 10 per cent nickel sulfate solution were invariably present. These authors were able to restudy forty of their original 198 patients. Of these forty patients, thirty-six of them retained their allergic sensitivity to nickel sulfate for periods of from two to seventeen years. The four patients who had apparently lost their sensitivity to nickel had been seen a few years prior to this follow-up. Some of the patients were patch tested with nickel coins, and all showed erythema, edema and fine vesiculation at the site of the test. Patch testing with nickel coins, however, would be of no significance as far as sensitivity to nickel is concerned if the coins did not contain nickel. It must be remembered that during World War II the nickel coin did not contain this mineral but did contain silver, copper and manganese. All of the patients sensitive to nickel were tested by these authors for their reaction to potassium dichromate and for copper sulfate. None of their patients, however, showed any positive reactions with dichromate or cupric sulfate. Metallic nickel is

a very common cause of allergic contact eczematous dermatitis. The lesions may occur in almost any skin area, but the most common sites are the ear lobes, thighs, hands and wrists. These authors recommend a 5 per cent nickel sulfate solution for routine testing for sensitivity to nickel.

Hand Dermatitis.—Of all the acute, subacute and chronic dermatoses affecting the hands, contact dermatitis is one of the most common. Weber[104] defines contact dermatitis as an inflammation caused by direct action of various cutaneous irritants on the skin. The characteristics of the skin determine to some degree its defense against cutaneous irritants. The amount of melanin pigment in the skin is significant; and the hands, because they are always touching or handling something, are especially vulnerable. The weakest point in the skin of the hands or fingers, however, is the dorsal surface. In that area there are numerous openings of ducts and there are hair follicles. A predisposing factor to contact dermatitis is excessive sweating, since solid substances may become irritants when they go into solution. Sweating of the hands also leads to maceration, to change of pH and in some instances to the obstruction of the ducts. A dry skin, on the other hand, is more susceptible to contact dermatitis from solvents and soaps. Contact dermatitis is due either to sensitizers or to primary irritants which are nonsensitizers. This distinction, however, is nonessential since a cutaneous irritant can be both a primary irritant and a sensitizer. Factors other than cutaneous irritants may account for the initial lesions on the hands. Weber believes that insignificant trauma and minor injuries to the skin may be factors of influence, inasmuch as a patient's dermatitis may appear on or near the site of such an injury. Overtreatment of minor injuries of the hand is the beginning of contact dermatitis in about one-third of all inflammatory dermatoses of the hand. The common practice for mercurial preparations to be used in the treatment of minor injuries, the almost routine procedure of applying adhesive over wounds, the application of burn ointments and various other preparations account for a high percentage of such overtreatment. It is necessary for a patient with contact dermatitis of the hands to have a complete examination of his entire skin. One must always keep in mind the possibility that some other skin disease can be present along with the eruption on the hands or that the skin disorder may be only a symptom of a systemic ailment. The author's advice concerning treatment parallels that of previous reporters, in that wet dressings, lotions and bland ointments should be used in the acute, red, vesicular type of lesions.

That there is a specific cause or offending agent for each instance of contact dermatitis is the contention of Johnston and Cazort.[44] Though it is recognized that there may be complicating factors of infection, trauma or impaired circulation, there rarely are any sequellae. However, both complications and sequellae are usually inconsequential if the causative agent of the contact dermatitis is recognized at an early stage of the lesions. These authors have a few rules which they follow on the initial visit when a patient with contact dermatitis is seen. A thorough and complete history is all-important and must be all-inclusive. If the patient has not been under the care of a dermatologist, the following suggestions usually are made. The patient should use no medication or application that has not been prescribed by the physician. Soap is not to be used on an irritated area. Wet compresses are to be given for the acute stage

of the lesions. Antihistaminic preparations are not to be used locally under any circumstances, the so-called "caine" drugs are not to be used locally, and a grease should not be used in the acute stage. Johnston and Cazort also avoid sulfa drugs or penicillin preparations locally because of their high index of sensitization. They have found the steroid preparations to be wonderful adjunctive therapy, since these preparations do not interfere with patch test reactions.

An editorial[25] emphasizes that atopic dermatitis is an intimate and equally important part of the same basic situation as are hay fever and bronchial asthma. Dermatologists pay too little attention to the immunologic aspects of atopic dermatitis. At the same time, it is the failing of many allergists not to have the dermatologic point of view which is so necessary in dealing with any disorder of the skin. The allergist should not have too much faith in the immunologic approach. He should be aware and cognizant of measures of therapy other than desensitizing inoculations. The editorial suggests that every allergist who expects to treat atopic dermatitis should spend some time working in a dermatology clinic, since dermatology is a vital part of his practice. Atopic dermatitis is recognized to be one of the most complicated and obscure situations in all medicine. The editorial writer calls for zealous and concentrated research of the same type which is now applied to cancer in order that the baffling condition of atopic dermatitis may be corrected.

Nummular Eczema.—Nummular eczema has occurred most frequently in young adults, in the opinion of Weidman and Sawicky.[107] Lesions have persisted from a few days to thirty-five days, with the dorsum of the hands and fingers being the sites of most common involvement. There has been a noticeable aggravation of nummular eczema symptoms during the winter with spontaneous improvement being experienced by most patients during the summer seasons. Though most of their patients showed positive reactions to potassium iodide and potassium bromide, these reactions were not considered to be significant since patients with numerous other skin complaints showed similar positive reactions. Vioform or tar preparations seem to be the most satisfactory therapeutic remedies. Steroid ointments are more efficacious, particularly for short term therapy. The authors have suggested that nummular eczema may not be a disease entity in itself, but rather a symptom-complex with multiple etiologic factors.

Poison Ivy Dermatitis.—In answer to a question regarding prophylaxis of ivy poisoning, it has been stated[70] that the use of pentadecylcatchol for hyposensitization should be restricted to persons who are exceedingly sensitive. These persons probably have had repeated bouts of severe poison ivy dermatitis. In the individuals who are treated with this preparation, the initial doses must be very small in order to prevent local or systemic reactions. The injections must be continued over a period of at least two months. Significant hyposensitization has been reported to have been produced in this way. The difficulty with extracts prepared from poison ivy leaves themselves is that there has been no method of standardizing these preparations. The results, therefore, are exceedingly variable. Oral prophylaxis for poison ivy dermatitis is either not effective or too toxic for practical use, in the opinion of Gaillard.[36] He believes that the material now available for treatment of dermatitis venenata can be

classified in three general types of extract: (a) the poison ivy resin in alcohol, (b) the solution of the poison ivy resin in an oil such as almond or corn oil, and (c) the active principle of the poison ivy leaf in a pyridine-alum precipitate suspended in saline solution. In his experience, the alum-precipitated pyridine ivy suspension in saline solution is superior to either the alcohol-ether or the oil absorption materials. In treatment, the highly sensitive individual can be desensitized by receiving subcutaneous injections at seven to fourteen day intervals of gradually increasing dosages of this suspension. The usual dosage schedule shows the amount and dilution to be as follows: 0.2, 0.5, and 0.8 ml of the 1:50 dilution followed by 0.2 and 0.5 ml of the 1:5 dilution of this preparation. This alum-precipitated extract is a repository material which, because of its insolubility, is slowly absorbed. He believes that prophylactic therapy for poison ivy dermatitis is simple and effective with oral or parenteral administration of adrenocorticotrophin hormones. At the same time, the topical use of adrenocorticosteroids for rhus dermatitis is unsatisfactory. The alum-precipitated pyridine ivy preparations suspended in aqueous solution has been named Aqua Ivy. All previous ivy extracts used either an oil or alcohol as the vehicle in which the oleoresin was dissolved, but this preparation contained the active ivy principle as an alum-precipitate suspended in a water solution. Passenger, Spain and Strauss[60] found that guinea pigs remained completely normal throughout the test period in toxicity studies with Aqua Ivy. The authors recommend active treatment of poison ivy dermatitis with essentially the same schedule as above reported for this preparation. It should be repeated every four to eight weeks. It is their opinion that the current therapy of choice for dermatitis venenata is systemic hydrocortisone for the severe acute lesions and Aqua Ivy for subsequent prophylaxis.

Wiseman and Adler[111] have proposed a new technique of testing for drug sensitivity which may be especially valuable in the study of patients with physical allergy due to chemical sensitivity. Their patient was a thirty-five-year-old man with a history of recurrent attacks of urticaria over a period of the previous four years. They were able to determine that his recurrent hives were due to cold sensitivity; and the mucous membrane hypersensitivity to cold of four years' duration resulted from a sensitivity to acetic acid. Direct skin testing of this patient with 0.1 per cent of chemically pure acetic acid was negative. When an ice cube was placed immediately over the test site for fifteen minutes, an urticarial reaction was obtained. Subsequently, ice cube tests over the untested skin and over an area tested with 1 per cent chemically pure lactic or citric acid were negative in their response. The authors suggest that in the presence of cold the acetic acid may act as a hapten to form a complex antigen responsible for the allergic reaction, or the cold may act as a more suitable medium to permit the acetic acid hypersensitivity to take place. In this respect, therefore, the cold could have been a catalyst in the allergic reaction.

Fungus Identification.—Approximately 30 per cent of the patients seen in average dermatologic practice have either an eruption due to one of the pathogenic fungi or have a condition that simulates a fungus infection. Robinson, Cohen, Robinson and Bereston[76] believe that many erroneous diagnoses have been made on clinical grounds alone without resorting to the use of scrapings or cultures or direct examination. Microscopic

identification can be facilitated by the use of an ink-potassium hydroxide stain. This is prepared by mixing equal parts of 20 per cent potassium hydroxide solution with Parker's Superchrome blue-black ink. The mixture can be stored in a 1 ounce eye dropper bottle and used as needed. This formula can be employed in staining scales, vesicle tops, nails, hair, and exudates. The technique for the use of this stain is as follows: scales, vesicle tops, nails, hair or hyperkeratotic material are placed on a clean glass slide to which a drop or two of the above stain is incorporated with the material. This is mixed well and covered with a cover glass. Microscopic examination is made using first low power and then high power objectives, if necessary. Some clearing will result if the preparation is allowed to stand for one hour before examination. This technique has been successfully employed in the demonstration of fungi from dermatophytosis, tinea cruris, tinea circinata, onychomycosis, tinea capitis and blastomycosis.

Industrial Dermatitis.—Weber[105] contends that a medical problem of considerable magnitude is industrial dermatitis. Some nonoccupational dermatoses may predispose individuals to occupational dermatitis. He believes that primary irritants represent about 25 per cent of the actual causes of occupational dermatitis. Trauma and accidental injury make up about 20 per cent, and sensitizing substances are present in about 18 per cent of the cases of occupational dermatitis. A primary irritant causes mild to severe inflammation as evidenced by redness to ulceration. The principal sensitizers are dye intermediates, photo developers, rubber accelerators and anti-oxidants, insecticides, fungicides, cosmetics, coal tar and its derivatives, explosives, plasticizers, plants and many others. The most common cutaneous hazard acting upon the skin externally is water. The palms are affected with maceration first because they lack the protective coating of sebum. Dermatitis in workers at so-called wet jobs constitute a daily problem in almost any dermatologic practice. If dryness of the skin is not maintained, many cutaneous diseases cannot be treated successfully. Wet work will also enable pathogenic microorganisms to gain a foothold during the healing of a wound or during the course of any dermatitis. Overtreatment is frequently a cause for the presence, for the severity, or for the persistence of a dermatosis. The avoidance of overtreatment is a cardinal principle in treating diseases of the skin. Successful management of occupational dermatitis depends primarily upon an accurate diagnosis and upon determination of the cause and any contributing factors. Briefly, the therapy for occupational dermatitis consists of mild and soothing applications. Preventive measures are more successful than treatment in reducing the disability from industrial dermatoses.

Hennington, Kennedy and Williams[42] remark that primary irritation rather than sensitization causes the cutaneous disorder in four out of five instances. They believe that the most common skin problems in industry are dermatitis which results from chrome, rubber or shoes. Chloracne is commonly found. The prevention of chrome dermatitis can be accomplished by the use of long rubber gloves or protective creams. Sodium bisulfite 5 per cent is recommended for cleaning the hands, since the solution reduces hexavalent chromate to trivalent compounds which are less injurious to the skin. Most rubber compounds are nonirritating after vulcanization. However, finished rubber products, such as gloves,

sponges, and elastic in clothing, may be responsible for sensitivity. Contact dermatitis due to shoes is frequently caused by sensitizers in the rubber in the shoes. The accumulation of moisture is also an important factor in irritation from shoes. Moisture repellent shoes prevent transference of psychic and thermal sweat. In workers exposed to insoluble cutting oils used on machine tools, chloracne is most common and is caused by chlorinated hydrocarbons. In the prevention of this condition, manufacturing processes involving chlorinated hydrocarbons should be enclosed as often as possible. Impervious sleeves and aprons are recommended. Affected workers should use cleansing agents often. Roentgen therapy is seldom an advisable procedure.

Piromen Therapy.—It is an accepted fact that the etiology and pathogenesis of many skin diseases are obscure. The long term management of these conditions is a frequent problem for all physicians who are concerned with dermatologic problems. Guy and Green[39] state that animal studies have indicated Piromen® to be an endocrine stimulant which acts primarily, though not exclusively, through the pituitary-adrenal axis. They studied cases which were inveterate and of long standing and which had failed to respond to usual dermatologic measures. They included in this study group those patients which traditionally are believed to respond to fever therapy. Their patients were divided into two groups, with half of their sixty-nine selected cases receiving Piromen, and the other half receiving isotonic saline placebo. No desensitization or avoidance procedures were attempted, though all of their patients had had complete allergy work-ups. Of twenty-eight patients treated with Piromen, seventeen showed good improvement, seven showed no change and four became worse. In a parallel study with control patients, of the fifteen treated with placebo, two were improved, eight showed no change and five became worse. No side effects were apparent when the drug was given subcutaneously in doses up to 20 gamma. Intravenous administration of the preparation produced occasional chills and malaise. They could find no apparent advantage in the intravenous administration of Piromen. Their results were not enhanced by resorting to high dosage in those instances failing to respond to routine dosage levels.

Welsh and Ede[108] found no evidences of systemic reactions with the administration of Piromen to their patients. Some of their patients reported an after feeling of well-being. No such report was given by any of their patients who received placebo administrations. They had 412 patients with infectious eczematoid dermatitis receiving therapy with Piromen as an adjunct to the other treatment measures that were employed. Of this group 356 patients showed greater improvement on therapeutic regimens including Piromen than on identical regimens without Piromen. Of the eighty-five patients studied with atopic dermatitis, sixty-eight of them showed greater improvement on the plus Piromen routine. Of twenty-three patients with urticaria and angioedema, thirteen of them received greater improvement when Piromen was added to their treatment routine. Based upon their observations, these authors show Piromen is not contraindicated in older patients. They found this preparation to be an effective adjuvant to appropriate conventional therapy in dermatoses which are involved with an allergic factor.

Abramson[3] reports a case illustrative of the role that emotional tensions play in the intensification or production of childhood eczema. On the

basis of interviews with the child, it was brought out that a traumatic event had occurred with the brother when the bowel movements were first retained. This patient's eczema cleared completely six weeks after the psychologically traumatic event was acted out during her therapeutic observation. In this particular incident, Abramson believes that the allergic components were negligible when compared with the psychogenic forces.

GASTROINTESTINAL ALLERGY

The etiologic association between an offending food and the clinical condition is easy to prove when the history is suggestive of the association, when positive skin test reactions to the offending food are found, and when circulating antibodies to the offending food are present. However, this is not true of all clinical manifestations ascribed to food allergy, particularly if the skin test reaction to the suspected agent is negative. Tuft and Ettelson[101] report a patient in whom recurrent outbreaks of canker sores, ascribed at times to food allergy, seemed to be associated with an abnormal reaction or allergy to weak organic acids, such as citric and acetic. It was demonstrated that the patient had a definitely abnormal reaction to citric acid and to foods or drugs containing this preparation. It is recognized that substances such as citric or acetic acids are nonantigenic, but the authors believe that they are correct in their designation of this as an allergy to weak organic acids. They emphasize the importance of a thorough study for these allergic patients in that often the clinical history might suggest that the symptoms are functional or psychosomatic. They had treated their patient for nasal allergy and for migraine for many years. Clinical investigation indicated that the recurrent attacks of oral canker sores were due to the presence of citric acid in food and drugs. Avoidance of foods containing the positive reactors resulted in marked relief, not only of the canker sores but also of the general symptoms which made the patient feel "toxic," which symptoms had previously been regarded as functional in nature.

The symptoms of gastrointestinal allergy vary greatly depending upon the portion of the alimentary tract brought into reactivity. Fries[35] groups the symptoms into patterns or syndromes not commonly characteristic of disorders on a hypersensitive basis. Because of the varied symptomatology which is seen in gastrointestinal allergy, organic disease and psychic causes must be ruled out even before hypersensitivity can be considered. Cutaneous tests are of limited value as a diagnostic assistance in gastrointestinal or food allergy. It is helpful to have other evidences of allergy in the establishment of an allergic etiology for gastrointestinal complaints. The presence of other obvious concomitant allergic manifestations, positive cutaneous tests, confirmatory roentgenograms and other evidences of allergic disease help to establish an accurate diagnosis. Therapy in gastrointestinal allergy is ideal when the offender can be identified and completely avoided. It is important that the physician must not fail to include suitable substitute foods to meet vitamin and nutritional requirements when he places a patient with gastrointestinal allergy on a strict elimination routine. Fries believes that hyposensitization by injection of an extract of the offending food is not only hazardous but has not proved effective. Oral desensitization has been unsuccessful in his experience. He concludes that gastrointestinal allergy is not as frequent as the liberal use of

the term today would imply. This condition occurs most frequently in children as an expression of food hypersensitivity.

Allergy and Diarrhea.—Rowe and his associates[78] report diarrhea from food allergy in twenty-six adults and four infants and children. Milk allergy by far is the most frequent cause of allergic diarrhea. In their experience, allergy to milk is more common than to any other food as a cause of the many manifestations of food allergy. They have not included any cases of chronic ulcerative colitis or regional enteritis in this report. Of the patients studied, no patient was included who had less than three stools. Most of their patients had three to ten stools daily. In this series, blood in the stools was absent. In fourteen patients, diarrhea was the only evidence of gastrointestinal allergy; but in sixteen others one or more of the following symptoms occurred: distention, burning and pressure in the epigastrium; belching, sour stomach, nausea and vomiting; canker sores and other symptoms and signs directed at the small bowel and the large bowel as the shock tissues. These authors believe that canker sores are nearly always due to food allergy. Although food allergy was the cause of the diarrhea in all of the patients reported by these investigators, scratch skin test reactions were negative in twenty-five cases. This is the usual rule in chronic food allergy. Before a diagnosis of allergic diarrhea can be made, it is necessary to carefully exclude the presence of parasites, infection, nutritional deficiencies, sprue, new growths and certain chronic diseases. If the diarrhea is nonseasonal in its presence, food allergy is a more likely cause. The control of allergic diarrhea is dependent on the continued, strict elimination of allergenic foods. They were disappointed in the results obtained with attempted desensitization by the oral method.

Roberts[75] presents two case reports illustrative of severe gastrointestinal wheat allergy. His one patient was a baker by trade, whose symptoms appeared only if wheat were ingested, but exposure to wheat flour during the course of his occupation produced no symptoms of any consequence. This was true as long as he maintained his wheat-free diet. His other patient had severe primary sprue which had become refractory to vitamin B_{12}, folic acid and cortisone acetate. The institution of a wheat-free routine in this patient produced a complete freedom from the symptoms of severe diarrhea.

Regurgitation.—The apparent relationship of allergic regurgitation and colic in the infant to hay fever and asthma in the older child and adult has drawn the attention of Schoenkerman.[82] He studied the results of a simple and rational method of allergic management for the prevention and treatment of these early symptoms. He placed eighty-eight infants with persistent regurgitation of virtually all feedings on a diet consisting of soy bean milk. Complete elimination of all other substances, whether food or medication, was accomplished. An arbitrary period of four days was chosen for maintenance of the patients on this soy bean diet. At the end of that time, other items were reintroduced in groups of two or three at each visit. Wheat, egg and milk were introduced later than other foods, since it was considered that these were potentially allergenic foods. Of the original eighty-eight infants observed by Schoenkerman, fifty-five stopped regurgitation immediately upon being placed upon the new routine of soy milk and water only. On re-establishment of a complete

diet, he was able to determine that forty-seven again began to regurgitate with the re-institution of milk, three with orange juice, three with wheat, one with egg and one with the vitamin preparation which the child was taking. Of the entire group, just under 55 per cent were proved to be sensitive to milk. He concludes that breast feeding, food rotation and the removal of proven allergens would appear to be the most valuable aids in caring for the infant with early symptoms of allergy. These measures also tend to prevent the later, more serious complaints. Three thousand infants and children in private pediatric practice have been studied from the point of view of milk allergy by Collins-Williams.[20] Of these cases, only nine patients with definite milk allergy were discovered, giving an incidence of 0.3 per cent. Though this is a recognized low percentage, that fact in no way detracts from the importance of milk sensitivity. The correct diagnosis makes the difference between an acutely ill child and a relatively well child. Milk sensitivity should be considered by the pediatrician in the differential diagnosis of all the conditions attributed to milk allergy.

Eosinophilia.—A very high level of eosinophils (up to 97 per cent) persuaded Swinny[92] to report a case study of his patient. The only symptom of this patient was fatigue and the high percentage of eosinophils was obtained in rapid fashion after the ingestion of the allergenic material. Her only positive reaction on skin testing with major food and inhalant allergens was a 4+ reading to milk. This patient was placed on a milk-free routine by this physician, and after two weeks on this routine she returned for laboratory studies. At that time the blood count revealed 3,700,000 red blood cells, 18 per cent eosinophils and a leukopenia of 1,600 white blood cell determination. The remainder of the blood survey was essentially within normal limits. Two hours after the ingestion of two glasses of milk the count remained the same, except that the eosinophils had increased to 32 per cent. Later studies revealed that the patient had remained well as long as she avoided milk products, but exhaustion and malaise were present if she partook of these foods.

Once a specific food sensitivity has developed, it may remain at a constant level for long periods or it may pass through one of several stages. The intake of the foodstuff in question appears to be a major determinant of the subsequent course of events. Two important aspects of this intake which have a definite bearing on the process are frequency of use and the size of the dose. Randolph[73] feels that these latter two aspects are of prime importance in determining the timing of onset of symptoms following the ingestion of an offending food. Quantitative aspects of dosage in food sensitivity are principally concerned with the rate of absorption from the alimentary canal. A patient is apt to have an immediate reaction after the ingestion of any particular food to which he is highly sensitive if it is taken only occasionally. In contrast to the ordinary concept of food allergy, the chronic cumulative use of a food to which one is highly sensitive is likely to be associated with an entirely different pattern, in that the symptoms are timed to occur in relation to the meals. Randolph labels the characteristic absence of immediate post-meal reactions as food addiction and that characterized by immediate post-meal reactions as food sensitization. He feels that this type of food sensitivity characterized by an absence of immediate postmeal reactions —termed by Randolph to be food addiction—is food sensitivity as it

most commonly exists. Most often involved are corn, wheat, coffee, milk, potatoes, eggs and other frequently eaten foods. Specific addictive sensitization to foods is believed by this author to be a major factor in the etiology of addictive eating and also addictive drinking. Alcohol may exert a drug or nonspecific action to which chronically exposed individuals presumably adapt in the sense of the general adaptation syndrome.

ALLERGIC HEADACHE

The characteristics of the onset of any headache may provide a clue to an allergic etiology. A personal history of allergic disturbances such as eczema, angioedema, urticaria, allergic rhinitis, and a strong family history of allergy, along with concomitant allergic complaints such as seasonal and perennial allergic rhinitis, are important features in this study as outlined by Carpenter.[15] He believes that the specific diagnosis must wait upon a determination of the degree of severity of exposure to specific allergens. The allergic load and the location of the allergic reaction in and around the head are important points whether the actual cause of the headache be vasodilatation, edema or something else. Carpenter believes that the diagnosis of inhalant allergic headache is made by: (a) a never ending suspicion of allergic etiology behind every functional headache, (b) a detailed and accurate history, (c) identification of the allergen by history and skin tests and (d) relief of symptoms consequent to specific avoidance and/or hyposensitization. The preferred treatment for inhalant allergy is, if possible, the elimination or avoidance of the offending allergen. In many instances, however, hyposensitization is in order because the patient is unable adequately to avoid or eliminate the causative factors. In addition to the elimination, control or treatment of the inhalant allergy, other concomitant sensitivities, especially food allergies, must be adequately treated. In the pre-edema stage of the acute attack, epinephrine 1:1,000 may control the vasodilatation. Carpenter has obtained good results by combining epinephrine with DHE-45, for they seem to enhance the effect of each other. In the edema stage of the acute attack, the preceding measures are usually ineffectual. Carpenter suggests the use of Neo-Calglucon 20 per cent given by the intravenous route. He believes that histamine is of definite value in the interval between headaches, and it should be given in a high dilution every three or four days. Some of the unsatisfactory results in the treatment of headache reflect a failure by the physician to recognize the presence of inhalant allergies.

Histamine and Head Pain.—Histaminic cephalalgia is a distinct clinical entity. Patients usually refer to their attacks as "head pain" rather than headache. Pain, the outstanding complaint, is usually steady, excruciating, burning and boring. There are no trigger areas, and the pain is not confined to the distribution of any cranial nerve. Horton[43] has found nausea, vomiting and cortical phenomenon to be usually absent. One of the main characteristics of histaminic cephalalgia is the tendency for the attacks to occur in a series which may appear to be upon a seasonal basis. Remissions and exacerbations occur spontaneously. Characteristic of this illness, too, are the night attacks which may occur with clocklike regularity. This author has employed the subcutaneous administration of 0.35 mg histamine base as a provocative test. This dosage will usually "trip the mechanism" in more than 60 per cent of the patients with these complaints. The immediate reaction after the administration of the histamine as a

provocative test is a generalized histamine headache. This is a physiologic response and usually has a duration of five to ten minutes. The term histamine headache and histaminic cephalalgia should not be regarded as synonymous terms. After the physiologic effects of the histamine have worn off, the patient feels normal. During this latent period some unknown mechanism is present so that about fifteen or twenty minutes after cessation of the histamine headache, a reproduction of the typical histaminic cephalalgia will be observed. In Horton's opinion histaminic cephalalgia appears to represent a localized and anaphylactoid reaction with both localized and systemic manifestations. The induced attack can usually be aborted promptly by the intravenous administration of dihydroergotamine methanesulfonate (DHE-45). The objective of treatment for patients with histaminic cephalalgia should be twofold, namely to alleviate the pain of the acute attack and to prevent any subsequent attacks. The use of oxygen by inhalation and intravenous administration of DHE-45 at the onset of the attack or shortly thereafter have usually been good agents of therapy. To prevent future attacks of histaminic cephalalgia, Horton's treatment of choice is histamine desensitization. He believes that histamine therapy is neither simple nor commonplace, that it is frought with many pitfalls and that it is difficult to outline a schedule which will fit any large group of patients. In other words, as in all forms of allergic therapy, the schedule of administrated medication must be individualized or tailor-made to fit each patient.

DRUG SENSITIVITY

Reporting Statistics.—Pertinent literature today presents the physician with four general types of drug toxicity-reporting. Brown[13] lists these as (a) epidemiologic studies of the incidence of drug reactions, (b) studies of series of patients treated with the drug, (c) case reports of one or of a few instances of such supposed drug reactions, and (d) reviews of such case reports. He believes that individual case reports misinform the physician to the extent that it is a matter of chance as to whether the cases have to be reported for publication, and if so, whether they are printed. On the basis of a recent Food and Drug Administration survey, quoted by Brown, acute anaphylactoid reactions to penicillin and other antibiotic agents were found to be about 30 per cent fatal. This reported survey elicited the fact that of the eighty-four such cases disclosed, twenty-four of the fatal cases had never been reported. Brown emphasizes the fact that such statistics are not clinically significant unless or until the physician has data on the number of patients exposed to the drug. He suggests that a better procedure of reporting reactions of all types would be to classify these reactions into such major groups as (a) very serious and potentially fatal, (b) major toxicity requiring cessation of treatment, and (c) minor reactions with elective continued treatment. Since some drugs are toxic and others nontoxic, this feature is dangerously disarming. The single case report or a collection of such single reports unintentionally tend to communicate the implication that the alternative drugs, by the mere fact that they are not discussed with equal emphasis, are in some way free of risk. It is necessary to know the frequency with which the physician may expect a particular type of reaction from a particular type of drug. Brown proceeds to describe what is really known regarding the available accurate information relative to reactions from

sulfonamides, penicillin, the anti-arthritic agents, and chlorpromazine. He believes that the information produces a pattern that is general even though it be not too satisfactory.

Penicillin Sensitivity.—Toxic and allergic reactions that accompany some of the new therapeutic products are considered as penalties of progress in therapy. Feinberg and Feinberg[32] illustrate this statement with a discussion on penicillin reactions. There are a variety of types of allergic reactions to penicillin. The cutaneous manifestations include urticaria, exfolliative dermatitis, contact dermatitis, erythema nodosum and multiforme, purpura and various rashes. However, the two most important allergic reactions from penicillin are the delayed serum sickness type and the serious immediate anaphylactic variety. These authors report that the serum sickness syndrome is much less frequently noted in children than in adults. It may occur on the first administration of penicillin, but more frequently it does appear in those who have had the drug previously. The likelihood of the occurrence of an allergic syndrome cannot be predetermined by a skin test, either of the delayed or of the immediate type. The disease cannot be curtailed by any known treatment, but the symptoms may be controlled by the use of antihistamines, the steroid hormones or corticotrophin. A fatal outcome is not rare in the patient with a severe anaphylactic reaction. Here, we see shock, nausea, vomiting, loss of consciousness, dyspnea or cessation of respiration. A large percentage of the severe or fatal anaphylactic reactions occur atopically in persons usually suffering from hay fever or asthma. The anaphylactic reactions occur most often when the drug is administered after an interval of weeks or months has elapsed since previous therapy. The original or sensitizing dose may be in the form of an injection, oral administration, aerosol inhalation, lozenge or topical application to the skin. The authors state that the allergenic quality of penicillin is not destroyed by heat. They emphasize that penicillin should be administered only when there is a clear-cut indication for its use. If the patient is known to be allergic, further inquiry is particularly indicated. Penicillin administration is a risky venture if there has been a suggestion of a previous immediate reaction. Feinberg and Feinberg advise that under such circumstances a skin test should be made consisting of a scratch test with a weak solution (about 5,000 to 10,000 units per 1 cc). If this is negative, an intradermal test should then be done using .01 cc of a solution containing 1,000 units of crystalline penicillin per cc. The vast majority of patients who react anaphylactically will show an immediate whealing reaction to this latter test. The allergic reaction of penicillin in a patient highly sensitive to the drug cannot be prevented by antihistaminic administration. In the case of an immediate reaction, the use of epinephrine should be given primary consideration. These authors call for the creation of a central agency where untoward reactions, both toxic and allergic, could be analyzed and reported.

Bierlein[10] states that severe anaphylactic shock precipitated by injected penicillin is becoming increasingly common. His case report shows not only some of the extreme dangers of use of the drug in sensitized individuals but also that the ordinary method of determining penicillin sensitivity by skin testing may produce fatal anaphylactic shock in highly sensitive patients. He states that ridiculously small amounts of penicillin have been known to produce fatal or near-fatal constitutional reactions.

He prophesies that poliomyelitis vaccine containing penicillin may be the source of anaphylactic shock or allergic reaction in those individuals sensitized to penicillin. Peters and his co-workers[63] report four patients developing anaphylactic reactions following the administration of penicillin. One of their patients was a fatality. The patient that expired became cyanotic unresponsive and expired within awenty minutes after the injection of 600,000 units of procaine penicillin. The other three patients became unconscious and went into shock following the use of penicillin tablets or troches. A mild constitutional reaction was experienced by one of their patients upon being tested by scratch test with dilutions of penicillin G. These authors emphasize that oral penicillin can produce anaphylactic reactions in highly sensitive individuals. They recommend the use of skin test detection as a screening method for potential reactors.

The examination of the peripheral blood of Paull's patient[62] revealed the presence of "LE" cells. The patient was under treatment for pulmonary emphysema, fibrosis, bronchiectasis, hypertensive heart disease and diabetes melitus at the time that he was admitted to the hospital by Paull with a diagnosis of pneumonia and congestive heart failure. Upon a subsequent readmission to the hospital, the diagnosis of drug reaction was manifested by urticaria, arthralgia of the joints, and a high elevation of temperature. Again the peripheral blood revealed the presence of "LE" cells. Paull postulates that there is a good probability that there is an immunologic mechanism responsible for the LE phenomenon which was observed in his patient with a severe penicillin reaction.

Prevention of Reactions.—Mathews and his associates[56] agree that skin testing is not generally reliable in the evaluation of the vast majority of penicillin reactions. The diagnosis of penicillin allergy usually must be based on clinical judgment. They have studied the question of antihistamines being used in the prevention of penicillin reactions. Over a period of twenty-two months every patient at the University of Michigan Student Health Center, for whom penicillin was prescribed, was sent to the Allergy Clinic to receive the drug. Before this was given, the patient was requested to take tablets designed to prevent penicillin reactions. The major portion of their study was designed so that the patients received in strict rotation fortified aqueous crystalline procaine penicillin G diluted either with physiologic saline solution or with a solution containing 10 mg of Chlor-trimeton®. Patients in each of these groups were given in rotation repeat action Chlor-trimeton tablets or similar placebo tablets to be taken three times daily for the duration of penicillin therapy and for ten days thereafter. Criteria for the diagnosis of penicillin reaction were (a) clinical manifestations of a type known to be related to penicillin allergy, (b) a satisfactory time relationship between these manifestations and penicillin administration and (c) the absence of other apparent causes for the observed reaction. Their tables and results show that an oral and/or parenterally administered antihistamine failed to produce any significant effect on the incidence of delayed or severe penicillin reaction. There did seem to be a reduction of early reactions, particularly those characterized by urticaria.

Coleman and Siegel[19] also studied the influence of parenterally administered antihistamines on penicillin hypersensitivity. These authors resorted to passive transfer studies performed on normal subjects with the use of a reagin-bearing penicillin-sensitive serum obtained from a

patient who had experienced two severe, immediate anaphylactic type reactions. They have reported that the addition of 10 mg of Chlor-trimeton to 300,000 units of procaine penicillin G failed to prevent the flaring of sites sensitized with undiluted serum or with a 1:4 dilution. They find it apparent that antihistamine in the dosage generally recommended can have no pronounced prophylactic effect against immediate constitutional reactions when therapeutic doses of penicillin are employed. There is very little reason to expect, therefore, that a mixture of antihistaminic drug with penicillin would prevent a severe, immediate allergic reaction upon the administration of the admixture.

Prednisone vs. Cortisone.—Feinberg and Feinberg[29] compared prednisone with cortisone as to the potency and side effects in eight patients with allergic disease. Many of these patients had been on cortisone therapy previously. In these patients, maintenance dosages of the two steroids were compared. No supplementary potassium was given, and sodium restrictions were not observed in the majority of instances. Of fifty patients with chronic perennial asthma, forty-one had good results on prednisone therapy. Twenty-seven of thirty-two patients with seasonal allergic rhinitis showed good results. Seasonal bronchial asthma responded in 100 per cent good control. It was the general impression of these authors that the initial dose of prednisone required is about 20 per cent of that of cortisone. Side effects and untoward reactions were essentially the same with each drug with the exception of sodium retention and edema. A change from cortisone to prednisone produced obvious elimination of edema and weight losses in two patients. The authors feel that prednisone is five or more times as potent as cortisone, with side effects being essentially the same.

In the treatment of patients sensitive to poison ivy, Kligman and Epstein[48] noted that about 15 per cent of their patients had adverse local reactions consisting of muscle pain, local soreness, swelling, tenderness and redness. To overcome this obvious objection, the authors hit upon the idea of incorporating corticosteroids into the pentadecylacatechol injection. They found that as little as 10 mg of hydrocortisone prevented or ameliorated adverse local reactions in most of their patients. Cortisone, in a dosage of 50 to 75 mg by mouth every day and maintained over a period of a month or more, adequately suppressed adverse local reactions at the injection sites. They state that the effects of hydrocortisone may not be comparable in this anti-inflammatory type of response to the characteristic atopic type of reaction seen in the allergic patient.

The administration of 10 mg of Chlor-trimeton® maleate by parenteral injection and followed by 8 mg of long-acting Chlor-trimeton orally every four hours is the treatment of choice for oral canker sores, according to Glasser.[37] Dramatic improvement has been noted within twenty-four hours after the institution of such therapy. Herpes zoster or herpes labialis responds in dramatic fashion. He suggests that other investigators administer antihistaminic therapy in the manner described by him in order to determine the effect in all diseases of viral origin.

Transfusion Reactions.—After studying 905 carefully selected patients who had received transfusions with whole blood, Winter and Taplin[110] conclude that allergic type reactions are about ten times more frequent in patients having positive allergic histories than among nonallergic in-

dividuals. Acute allergy transfusion reactions will occur in nonallergic persons, but in a ratio of about one in seventy. Chlor-trimeton effectively prevents acute allergic reactions, particularly if a 10 mg dose is mixed with the blood prior to its administration. This antihistamine, however, has no prophylactic value in reducing acute febrile transfusion reactions. Both types of acute transfusion reactions are effectively eliminated with a prophylactic regimen consisting of acetylsalicylic acid, .65 gram orally one hour before transfusion and repeated every three hours, plus 10 mg of Chlor-trimeton mixed with the blood. Prophylactic effect is obtained with 10 mg of the antihistamine, but smaller dosages which will prevent the acute allergic transfusion reactions have no effect upon the prevention of all reactions. The value of the antihistamine is enhanced if the dosage of the drug is mixed with the blood to be administered, since it is likely that adequate blood and/or tissue concentrations are maintained for a longer period of time. At present only a rare, acute reaction to transfusion is proved to be caused by hemolytic factors. A large reduction in non-hemolytic reactions will reduce, therefore, the number of unnecessary blood samples returned to the laboratory for retyping and other time-consuming procedures. True immunologic reactions will also be pinpointed by the procedures outlined by the authors.

Fasting donors have not reduced to any degree the incidence of the allergic type of reaction, according to Seldon.[83] Urticaria has been listed by him to be the second most common complication in blood transfusions. Allergic reactions were associated with 1.3 per cent of the transfusions noted by this author during the year 1954. The most common complication of blood transfusion is the hyperthermic or pyrogenic type of reaction which is characterized by chills and fever. These reactions appear during or a few minutes after the transfusion. In the allergic type reaction, epinephrine hydrochloride may be administered unless this drug is contraindicated by the patient's physical ailment. Treatment for the hyperthermic type reaction is purely symptomatic. The transfusion need not be discontinued, depending upon the severity of the reaction. Seldon suggests that for future transfusions, epinephrine, codeine or one of the antihistamines be added to the bottle or administered directly to the patient who has in the past, experienced an allergic type reaction from transfusion.

Chlor-trimeton was used by Sanger and Ehrlich[79] as an additive to contrast media in an effort to minimize the reactions to this dye. They did not exclude asthmatic and allergic individuals from their study, but undertook to include all patients who had had severe reactions during previous pylography. The administration of their contrast media was by the intravenous route, in a dosage of 20 to 25 cc to which was added 20 mg of Chlor-trimeton. This special mixture was given to 623 patients, with 379 individuals acting as controls and receiving the dye alone without the added antihistaminic preparation. Their contrast media was sodium acetrizoate or sodium iodomethanate. Allergic reactions were virtually eliminated by the addition of the antihistaminic preparation to the dye. No anaphylactic reactions occurred in the series injected with the mixture. With the technique described by these authors, patients who had had violent reactions on previous pylographies had little or no trouble. The overall reduction in reactions was fourfold, as reported by these two investigators.

Tranquilizers.—Adverse reactions have been reported after the administration of the tranquilizing drug, meprobamate, by Friedman and Marmelzat.[34] These reaction symptoms were listed as being of the following natures: cutaneous, muscular, gastrointestinal and paradoxical cerebral effects. The skin lesions, as a result of this drug sensitivity, seem to have a predilection for the pelvic girdle area, the breast area and the flexor surfaces of the arms. The trunk and legs are less commonly involved. It was not unusual to notice a patient develop a reaction within three to five minutes after taking one tablet even though he had had no previous experience of having taken the compound in the past. The authors believe that a possible explanation of this phenomenon is that patients had been exposed in the past to compounds which were chemically related to the drug in question. The patients reported by these men showed reactions characterized by intestinal hyperperistalsis with rice water stools, palsy of the extra-ocular muscles with diplopia, and skin lesions which were chiefly purpuric in nature. They state that the drug, meprobamate, has the potential of producing a number of diverse dermatologic patterns, but no mucous membrane lesions were observed. Theriault[95] has reported an incident of a patient developing a marked leukopenia to the use of chlorpromazine in a dosage of 300 mg daily. A white blood count revealed only 450 cells within forty-eight hours after the onset of an acute illness. This blood smear showed only lymphocytes to be present, and the cells were so difficult to find that a differential count could not be done. Severe jaundice and signs of kidney irritation were observed. The administration of whole blood, antibiotics and corticosteroids did not prevent the expiration of this patient within five days after the diagnosis of agranulocytosis was established. Theriault has stressed that patients using chlorpromazine should have frequent blood studies made in order to observe any departure from the normal picture.

Bernstein[9] reports another instance of anaphylaxis to heparin in a patient with multiple sensitivities. This occurrence of heparin anaphylaxis is supported by skin and passive transfer tests. Most commercial preparations of heparin are prepared from beef lung. Bernstein found skin and passive transfer studies in his case to be positive for the beef heparin preparation. The same tests were negative for pork heparin. Negative reactions were also determined for simultaneous testing with pork, beef, and beef serum antigens. The prompt use of epinephrine may have been life-saving in this patient. The use of this drug may have been considered to be radical because of a history of myocardial infarct in the patient. The author suggests that he may have been wise to use a skin test with heparin prior to the intravenous use of this preparation. He advises that caution be exercised in the employment of heparin therapy in allergic patients.

Parenteral thiamin chloride injections rarely cause reactions with any serious consequences. Tetreault and Beck[94] report a severe reaction in their patient following the intramuscular injection of thiamin chloride. They find their patient particularly interesting because he fulfilled the necessary criteria for anaphylaxis and subsequent shock, namely: (a) intramuscular thiamin chloride had been given prior to the last acute episode and presumably sensitized the patient, (b) there was a period of latency for antibody production, and (c) he was inadvertently re-exposed to the same potential allergen by the same parenteral route wherein the patient developed shock symptoms. Their patient received seventeen injections of liver parenterally over a one month period, during which time

he suffered an acute reaction when a concentrated solution of thiamin was given intramuscularly. They postulate that perhaps he should be considered as having manifested cumulative toxic effects from thiamin as a result of his multiple liver injections.

Phenindione has proved to be a satisfactory oral anticoagulant. Pastor and Tetreaut[61] have observed a severe agranulocytic reaction to the drug. Associated with the blood dyscrasia was a diffuse scarlatiniform eruption, which induces them to re-emphasize the potential toxicity of this drug. They were unable to prove definitely that phenindione was responsible for the agranulocytosis in their patient, because they were reluctant to attempt a reproduction of the blood picture by giving the drug a second time. Since this drug is used widely in myocardial infarction and thromboembolic disease, they warn against the possibility of overlooking a drug reaction from this source because the physician may be unaware of the potential risk. If infectious complications of agranulocytosis cannot be controlled, the disease may be fatal even though steroid therapy has recently proved to be a marked factor in the better prognosis associated with this condition.

It is somewhat rare to have an anaphylactic type reaction follow the oral ingestion of iodide-containing cholecystographic media. Cohen and his associates[18] have reported such a case, pointing out that this apparently rare but potentially serious manifestation of hypersensitivity should be considered prior to the administration of this preparation. The material used by the authors is rapidly absorbed from the gastrointestinal tract into the blood stream, and therefore an anaphylactoid reaction is entirely possible when the blood concentration reaches a critical level in a highly sensitive patient. This patient had had previous use of the iodide-containing contrast medium without any untoward reaction having been noted. Seven years prior to the reaction an intravenous pyelogram had been done, and three years previous to the exposure and reaction to the iodide-containing medium, a cholecystogram had been completed. It is probable that these previous exposures served as the sensitizing mechanisms. It is entirely possible that the reaction resulted from a hypersensitivity to the iodoalphionic acid specifically or to some other radical of this compound rather than the iodide portion. Complete recovery was obtained in this patient with prompt use of epinephrine, parenteral antihistaminic preparations and the adrenal corticosteroids. The authors were unable to demonstrate circulating reagins against iodide and iodoalphionic acid.

Transient Myxedema.—It is unusual to see clinical manifestations of iodide effect on the function of the thyroid gland in those patients who use iodide preparations for a prolonged period of time in the treatment of bronchial asthma. Skaggs and Cooke[86] have reported an unusual patient with a definite transient myxedema due to prolonged ingestion of saturated solution of potassium iodide. Even with the extensive and prolonged use of iodide preparations in the treatment of asthma, very few resultant goiters or evidences of myxedema have been observed. It is not definitely recognized how thyroid function is suppressed by an excess of iodides in certain patients. The authors eventually postulate that the thyroid gland of their patient was incapable of responding to endogenous thyrotropic hormone through some action of the iodide. They administered the thyrotropic hormone in an attempt to distinguish primary and secondary hypothyroidism.

Aspirin Substitute.—It is often difficult to obtain a satisfactory analgesic-antipyretic preparation in those patients with a sensitivity for aspirin. Cornely and Ritter[22] report upon the antipyretic effectiveness of Tylenol, and elixir which contains 120 mg of N-acetyl-p-aminophenol per 5 cc. The antipyretic response with this preparation in twenty patients was good to excellent in 90 per cent, and the analgesic effectiveness was considered to be good in sixty-eight of 121 patients. Prolonged administration of the preparation produced no undesirable side effects nor were any effects noted upon the hemoglobin concentration, total white blood cell count or differential leukocyte count. They conclude that as a result of the clinical observations upon 141 infants and children, Tylenol elixir was well accepted and well tolerated by these patients. It may be wise to remember that this preparation can be used as a substitute analgesic and an antipyretic in those patients who are aspirin-sensitive.

Though sulfisoxazole (Gantrisin®) is reported to be one of the safest of the sulfonamids, Green and Early[38] call attention to the fact that thrombocytopenic purpura may result from the use of this drug. They report two instances in which the administration of this preparation resulted in a serious complication of thrombocytopenic purpura. Their first patient recovered rapidly without any serious hemorrhagic difficulties. Numerous transfusions were necessary to sustain the life of their second patient. They warn against the indiscriminate use of this drug and suggest that it be used only where adequate indications are present.

Aminophyllin Toxicity.—In a child who has received one or more doses of aminophyllin, intoxication from this drug should be suspected whenever excitation, irritability, vomiting, muscle twitching or pallor are observed. White and Daeschner[109] state that symptoms of central nervous system irritability are very common associates of aminophyllin intoxication in children. It is suggested that the dosage of this drug be 3.5 mg per kilogram of body weight for intravenous or intramuscular administration, 5 mg per kilogram for oral administration and 7 mg per kilogram for administration as a rectal suppository. More than these suggested dosages may lead to severe symptoms and massive gastrointestinal hemorrhage which may be fatal. The dosage suggested should not be repeated more often than every six hours. The authors remind us that small doses of ephedrine seem to potentiate the toxicity of aminophyllin.

Similar reports are published by Nolke[58] who found severe toxic reactions with the use of aminophyllin suppositories in thirteen children, eleven of whom were asthmatics. Four of these thirteen children were fatalities. Central nervous system irritability was also found in these patients as early symptoms of toxicity. In the end stages, a state of delirium and coma with convulsions, hyperthermia, profuse diaphoresis and finally vasomotor collapse were observed. It seems quite alarming to report that toxic symptoms occurred after the first suppository in four patients and with the second suppository in ten instances. In the majority of patients, the doses of the suppositories could be regarded to be within the therapeutic range, and the dose was not considered to be excessive. Autopsy findings revealed esophageal ulceration with perforation in two cases and pulmonary inflammatory changes in all instances. Because of the unpredictability of absorption, Nolke has concluded that rectal suppositories are a poor means for the administration of aminophylline.

Most of the adverse reactions to isonicotinic acid hydrazide have been limited to the central and peripheral nervous systems and are evi-

denced by muscular twitching, irritability, peripheral neuritis, convulsions and psychoses. Walsh, Linn and Derbes[102] have reported pyrexia as a manifestation of hypersensitivity to this drug even though it is rather uncommonly observed. In their patient, a nine-day incubation period was present, which condition in itself was highly suggestive of other allergic febrile conditions. Pyrexia in their patient was observed on three occasions with the institution of isonicotinic acid hydrazide therapy. On each occasion the elevated temperature subsided promptly with symptomatic care and discontinuation of the drug. Though uncommon, the pyrexia reactions to this preparation should not be considered as rare. Consideration should be given to almost any drug as a cause of pyrexia.

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1320 Second Avenue S.E.

THE FETISH OF EXPERIMENT

Longfellow wrote: "I shot an arrow into the air, /It fell to earth, I knew not where . . . /I breathed a song into the air, /It fell to earth, I knew not where." We like this carefree attitude, but some people who have good songs to breathe seem unable to go about the task so light-heartedly. They feel compelled to have a control group of poets who do *not* breathe songs into the air; they consider it necessary to conduct a survey to determine the differential effects of song-breathing and nonsong-breathing poets; and they need the assistance of a committee of experts to advise on the proper methods of evaluating the data obtained in the survey. . . . —Editorial, *Science*, 125:177, 1957.

Editorials

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

NEW DRUGS (1956)

In his annual study of new prescription drugs, Paul de Haen reports on 401 new drugs made available to physicians in 1956. In 1955 there were 403. The cumulative nine-year total is 3,286.

The more important groupings into which the new drugs can be placed include laxatives, hypotensive and ataractic drugs, antispasmodics, antibiotic and antihistaminic agents and hormones.

If there is an archetype in the minds of the drug manufacturers, he is an overweight, constipated, hypertensive male suffering from metabolic insufficiency due to a poorly balanced diet. He is a latent diabetic with a questionable peptic ulcer, suffering from frequent colds on an allergic basis.

We can calm him mentally while we stimulate him metabolically. We can diminish his discontent with his obesity while we lessen the distress of his reduction diet. With vitamins, antihistaminic and antibiotic agents, we can lead him "beside calm waters." We can have him wide awake before he leaves his bed and sleepy before he gets to his bedroom.

At first it was the antibiotic agents which could be prescribed for all the ills to which flesh is heir. Now the ataractic drugs are suitable for use in multitudinous disorders.

The report prepared by a subcommittee on tranquilizing drugs at the request of the New York Commission of Health quotes from the literature sent physicians. The drugs are useful in ". . . hyperactivity, irregular sleeping habits, nightmares and homesickness in children; the very circumstances in adolescence which give rise to severe anxiety and tension; in adulthood, apprehension and anxiety over finances, effects of excitement or misfortune in the family such as sickness, accidents, weddings, funerals, separations and differing opinions.

"The drug is also said to be indicated in times of occupational stress: such as anxiety over interviews, competitive examinations, or public appearances; thus it is recommended for actors and actresses, radio and television performers, business executives, postmasters, ministers, teachers, professors and politicians.

"It is reported to be useful in the journalistic and advertising field with its tension, excitement and noisy environment. The indications also include competitive sports."

The committee brought to light twelve cases of poisoning in 1955 and seventy-six during the first ten months of 1956.

But in a more serious vein, how many allergists can distinguish between all the antihistaminic agents by whatever name known and, as well, between the mixtures in which they are contained?

How many physicians know the medical qualities of the 7,619 "new" products of which 3,286 are totally new products and 1,047 are new dose forms, with 333 new single chemicals and 875 duplicate products (single chemicals put out with differing names by two or more manufacturers) and, as well, 2,078 compounded products containing more than one active ingredient? The know-how that makes these drugs available should be able to work out a system by means of which their names, their indications and contraindications and side reactions can be presented simply and honestly and learned easily and well.

ANTIBODIES AGAINST ANTIBODIES

Dr. Nathan Kaliss of the Roscoe B. Jackson Memorial Hospital of Bar Harbor, Maine, has done an ingenious piece of work which may change present-day concepts of immunologic processes.

In essence, he has injected rabbits with extracts of mouse tissues. The antisera-containing antibodies produced by the rabbits against these mouse tissues were then injected into another strain of mice. These then produced antibodies against the rabbits' anti-mouse antibodies. When the second set of mice were injected with tissues from the first set, these tissues took hold and grew because the new hosts' resistance had been negated or neutralized by the antibodies produced. If carried to its logical extreme, this technique might help solve the problem of heterologous skin grafting and organ transplants.

If, as Dr. George D. Snell and his associates of the same laboratory have shown, it is true that cytoplasmic particles of a cell which overcome a foreign host's immunity are genetically controlled, the two discoveries have opened a door on a new view of the pathogenesis of cancer, allergy and a number of other, at present, puzzling diseases.

"There are people who are born with a certain sensitivity because of which, when entering a room in which a cat is present, an irritation results on the surface of their body which makes them rather uneasy. They are at first not aware of the cause of this condition and only repeated occurrence—with the aid of memory—makes them realize the object that creates the disturbance."—GEORG ERNEST STAHL (1660-1734), *Disquisition de Mechanismi et Organismi Diversitate,* 1706. (Submitted by Ernest Harms)

Papers of Interest

Bostock, J.: Asthma: A synthesis involving primitive speech, organism and insecurity. J. Ment. Sc., 102:559-575, 1956.

Asthma is regarded as an end-product of faulty respiratory maturation. For it to become manifest, there must be an organic reaction which triggers the infantile pattern, and an asthmagenic environment which keeps alive and accentuates the primal insecurity. Of 38 children studied, 37 presented a history of major respiratory tract infections, and one, dermatitis. In addition, 21 children responded allergically to various substances.

Papper, S., and Handy, J.: Observations in a "control" group of patients in psychosomatic investigation. New England J. Med., 255:1067-1071, 1956.

Twenty-five patients with infectious hepatitis, ten with pneumonia and ten with acute appendicitis were selected as a "control" group in the course of psychosomatic investigation. Their social difficulties and emotional problems were found to be similar to those described in many psychosomatic illnesses. The history of an acute emotional upset in the recent premorbid period was commonly elicited. It is concluded that "the mere presence of environmental handicaps, emotional problems and antecedent distressing emotional experiences in any patient group cannot be considered evidence or proof that these factors necessarily bear any etiologic relation to a pathological state."

Allibone, E. C.; Allison, P. R.; and Zinnemann, K.: Significance of *H. influenzae* in bronchiectasis of children. Brit. M. J., 1:1457-1460, 1956.

From bronchoscopic and antral washings of nineteen of thirty-two children suffering from bronchiectasis, *H. influenzae* was isolated. Treatment was with chloramphenicol (4 grams daily) and also with oxytetracycline or erythromycin combined with sulphonamides. Relapse was associated with reappearance of *H. influenzae* in half of the patients.

Bolande, R. B.; Schneider, A. F.; and Boggs, J. D.: Infantile lobar emphysema. An etiological concept. A.M.A. Arch. Path., 61:289-294, 1956.

In a sixteen-year survey of the records of the Children's Memorial Hospital of Chicago, seven true cases were discovered. The twenty-three cases previously reported in the literature are reviewed. A congenital "fibrous dysplasia" is suggested as an etiologic factor.

Kodolova, I. M.: Changes at different levels of the nervous system and in the lungs in bronchial asthma. Arkh. Patol., 18:73-82, 1956.

A histologic study of nerve morphology of four patients who died of bronchial asthma demonstrated major changes in pulmonary nerve fibres of medium and large diameter. It is suggested that the anoxia of severe asthma affects tissues of higher oxygen needs.

Wagner, H. N.; Bennett, I. L.; La Sagna, L.; Cluff, L. E.; Rosenthal, M. B.; and Mirick, G. S.: The Effect of hydrocortisone upon the course of pneumococcal pneumonia treated with penicillin. Bull. Johns Hopkins Hosp., 98:197-215, 1956.

In addition to routine measures, fifty-two of 113 patients suffering from pneumococcal pneumonia received five days of treatment with oral hydrocortisone. It is concluded that cautious use of steroid hormones as adjuvant treatment is justified.

Blodgett, F. M.; Burgin, L.; Iezzoni, D.; Gribetz, D.; and Talbot, N. B.: Effects of prolonged cortisone therapy on the statural growth, skeletal maturation and metabolic status of children. New England J. Med., 254:636-641, 1956.

In twenty allergic of thirty-six children observed, doses of 60 mg daily reduced rate of growth with compensation occurring when the dose was reduced. The ultimate height of growing children is evidently not affected.

Rich, A. R.: The pathology and pathogenesis of experimental anaphylactic glomerulonephritis in relation to human acute glomerulonephritis. Bull. Johns Hopkins Hosp., 98:120-151, 1956.

Rabbits injected with antigens free of primary toxicity developed as a result of anaphylactic hypersensitivity glomerular changes typical of human glomerulonephritis.

Frick, P. G., and Good, R. A.: Studies on agammaglobulinemia. VI. Hemostasis in patients with agammaglobulinemia. Proc. Soc. Exper. Biol. & Med., 91:169-172, 1956.

Agammaglobulinemia is probably due to a deficiency of one enzyme concerned with protein synthesis. The absence of gamma globulin does not affect blood coagulation.

Turiaf, J.; Blanchion, P.; Sauvan, R.; and Georges, R.: The treatment of chronic cor pulmonale in asthmatics with adrenocortical hormones (ACTH, cortisone, and cortisone derivatives). Bull. et mém. Soc. méd. hôp. de Paris, 72:188-216, 1956.

Successful treatment of four elderly male patients suffering from a severe combination of pulmonary disorders.

Stefanini, M., and Martino, N. B.: Use of prednisone in the management of some hemorrhagic states. New England J. Med., 254:313-317, 1956.

Among others, two patients with acute anaphylactoid purpura responded with apparent remissions. No response was noted in a patient with chronic purpura.

PAPERS OF INTEREST

Kourilsky, R.; Kourilsky, S.; Laurent, R.; Chevreau, J.; Brille, D.; and Hatzfeld, C.: Bronchillar disease in chronic pulmonary emphysema. Presse med., 64:324-328, 1956.

Following studies in depth of fourteen patients the importance of hypersecretion of pulmonary mucus as evidenced by expectoration is observed as proof of bronchiolar obstruction and alveolar degeneration.

Bates. D. V.; Knott, J. M. S.; and Christie, R. V.: Respiratory function in emphysema in relation to prognosis. Quart. J. Med., 25:137-157, 1956.

As a result of studying fifty-nine patients for more than three years, it is concluded that the best guide to prognosis is the measurement of the diffusing capacity of the lung as measured by the carbon monoxide uptake method.

Felix-Davies, D., and Westlake, E. K.: Corticotrophin in treatment of acute exacerbations of chronic bronchitis. Brit. M. J., 1:780-782, 1956.

The addition of ACTH gel (15 units/day for six days) to routine measures was of no apparent benefit to twelve of twenty-four patients suffering from acute exacerbation of chronic bronchitis.

Hellerstrom, S., and Lidman, H.: Studies of Besnier's prurigo (atopic dermatitis). Acta dermat.-venerol., 36:11-22, 1956.

Of 311 patients, only twenty-two failed to react to intradermal or patch tests. Sex distribution was equal. In eighty-six patients the disorder was apparent before the age of five. There was a 30 per cent familial incidence of bronchial asthma.

Buck, C.: Acute upper respiratory infections in families. Am. J. Hyg., 63:1-12, 1956.

In a study of forty-five families it was noted that pre-school and school children most frequently introduced colds into the household. The secondary attack rate is, however, affected by many factors.

Seneca, H.: *In vitro* and *in vivo effect* of metisteroids plus antibiotics or antibacterial on bacteria. Am. Pract. & Digest Treat., 7:1245, 1956.

Studies *in vitro* demonstrated that the steroid hormones depressed the action of bactericidal but not bacteriostatic antibiotic agents. They do not interfere with the effects of chloramphenicol, the tetracyclines, erythromycin, carbomycin, and novobiocin, among others. The effects of penicillin, streptomycin, polymyxin and neomycin are lessened.

Forbes, A.; Merlis, J. K.; Henriksen, G. F.; Burleigh, S.; Jiusto, J. H.; and Merlis, C. L.: Measurement of the depth of barbiturate narcosis. Electroencephalog. & Clin. Neurophysiol., 8:541 (Nov.) 1956.

The depth of barbiturate narcosis can be measured by means of respriatory rate and depth. This is satisfactory and inexpensive as compared to negative feedback from the electroencephalograph.

Feinberg, R. J.; Davison, J. D.; and Flick, J. A.: The detection of antibodies in hay fever sera by means of hemagglutination. J. Immunol., 77:279 (Oct.) 1956.

Antibody measured by adsorption of antigen on red cells treated with tannic acid proves them probably not identical with reagin.

Gore, C. P., and Biezanek, A.: Agranulocytosis during treatment with Pacatal. Lancet, 2:1081 (Nov. 24) 1956.

Another reaction from another tranquilizing agent! (Pacatal, 9-(1-methyl-3-piperidylmethyl) phenothiazine.)

Babione, R. W.: Penicillin reaction rates in relation to penicillin usage in the Navy. Antibiot. Med. & Clin. Therap., 3:388 (Nov.) 1956.

Rate of reaction to antibiotic dropped from 2.3 to 1 per 1,000 men in four years with decline in usage of injectable penicillin.

Sprunt, D. H., and Flanigan, C. C.: The effect of malnutrition on the susceptibility of the host to viral infection. J. Exper. Med., 104:687 (Nov. 1) 1956.

Respective increased and decreased viral susceptibility are related to fat and protein utilization.

Doust, J. W. Lovett; Husdan, H.; and Salma, M. E.: Blood-histamine and tissue-cell anoxia in mental disease. Nature, 178:492, 1956.

Patients with schizophrenia and epilepsy show a greater mean blood histamine level than do normal subjects. There is increasing evidence of the relationship between tissue anoxia, mental disease, and histamine release.

Breckler, I. Alfred; Hoffman, Milton, C.; Hill, Harry E.; Hensler, Nestor M.; and Hukill, Peter B.: Pleural biopsy., New England J. Med., 255:690 (Oct.) 1956.

In nine of ten cases (in whom tuberculous pleural effusion had been suspected) the diagnosis was confirmed by pleural biopsy as it was in two patients in whom intrathoracic neoplasm was diagnosed.

News Items

PAPERS FOR FOURTEENTH ANNUAL CONGRESS

The morning of the annual meeting during the Thirteenth Annual Congress of the College, devoted to the papers by Associate Fellows, was so enthusiastically received and attended by Fellows and guests that it will be repeated for the Atlantic City meeting to be held in April, 1958.

Associate Fellows are urged to begin preparation now for papers to be presented. The title and two abstracts of approximately 250 words should be submitted at an early date for consideration of the program committee. It is planned to limit presentations to ten or fifteen minutes. A prize, given by The Women's Auxiliary of the American College of Allergists, totaling $150, will be awarded to the best paper given.

Abstracts or finished papers should be sent to Merle W. Moore, M.D., Chairman of the Program Committee, Medical Arts Building, Portland 5, Oregon, not later than November 15, 1957.

PURPOSE OF THE NEW SESSION ON ALLERGY OF THE NERVOUS SYSTEM

The first session on Allergy of the Nervous System was held Friday morning, March 22, 1957, at the time of the Chicago meeting of The American College of Allergists. This was an outgrowth of an organizational meeting held at the time of the College meeting in 1955. At that time, Dr. Theron G. Randolph, Chicago, Illinois, was elected chairman, and Dr. Frederic Speer, Kansas City, Kansas, as secretary.

The purpose of the session is to bring to the membership of the College and other interested physicians clinical evidence bearing on the response of the brain and other parts of the nervous system to allergenic stimulation.

The recent half-day session is believed to have been the first such program to be held. The program outlined the historical development of the subject and placed particular emphasis on brain dysfunction or cerebral manifestations resulting from particulate inhalants, foods and diverse petro-chemical or hydrocarbon exposure. What is known of mechanisms involved was also presented.

The program for 1958 will emphasize the clinical problem of headaches of allergic origin and the clinical manifestations of allergy as manifested by the peripheral nervous system. Fellows are urged to keep this in mind and to submit brief reports of illustrative cases. Other suggestions for the program will be appreciated.

At the business meeting immediately following the scientific program, Dr. Frederic Speer was elected chairman and Dr. C. R. Ahroon of Bloomington, Illinois, was chosen co-chairman and secretary.

STORM VAN LEEUWEN MEDAL

With a view both to honor the name of the great Dutch allergologist Storm van Leeuwen and to express its great appreciation of the work done by other allergologists, the Dutch Allergy Society has decided to institute the "Storm van Leeuwen Medal." This medal will be awarded once every five years and the recipient will be invited to speak about his work. The Storm van Leeuwen Medal will be presented for the first time in May, 1958. In view of his splendid achievements in the field of allergology, the members of the Dutch Allergy Society have requested Dr. F. M. Rackemann, Boston, to accept this medal.

WOMEN'S AUXILIARY OF AMERICAN COLLEGE OF ALLERGISTS ANNOUNCES PLANS FOR 1958

Announcement of plans for the coming year has been made by the Women's Auxiliary of The American College of Allergists, following its third annual meeting.

The Auxiliary has pledged to give $500.00 to the Association of Allergists for Mycological Investigation for the pursuit of its program in mold allergy investigation. It will also provide $300.00 for six scholarships to the Instructional Course to be given by The American College of Allergists in Atlantic City, April, 1958.

The two awards given by the Auxiliary will also be continued. One of these, the Clemens von Pirquet Award, named for the "father of allergy," is given for the best paper written by a student or intern on any aspect of allergy. The 1957 Award was won by Mr. Donald Schaffer, senior student at the University of Buffalo Medical School. The other, the Bela Schick Award, is given for the best paper presented by an Associate Fellow of The American College of Allergists during the Congress. The paper by Dr. Clyde K. Walker of Canfield, Ohio, was voted the winner by the Fellows present. Both awards consist of cash prizes and Certificates of Merit.

Three new Board members were elected by the Women's Auxiliary during their convention meeting: Mrs. J. A. Blue, Oklahoma City, Oklahoma; Mrs. J. A. Mansmann, Bakerstown, Pennsylvania, and Mrs. B. Pool, Winston-Salem, North Carolina.

INTERNATIONAL ASSOCIATION OF ALLERGOLOGY

The dates of the Third International Congress of the International Association of Allergology have been changed to October 19-25, 1958. As planned, the meeting will be held in Paris, France. Details may be obtained from the Secretary-General, Dr. José Quintero Fossas, Paseo 313, Vedado, Havana, Cuba. Letters concerning non-secretarial matters can be directed to the President, Dr. Samuel M. Feinberg, 303 East Chicago Avenue, Chicago 11, Illinois, or to the President-Elect, Dr. Bernard N. Halpern, 197 Boulevard St. Germain, Paris VII^{e}, France.

LOS ANGELES SOCIETY OF ALLERGY

At a recent meeting of the Los Angeles Society of Allergy the following officers were elected for 1957:

D. E. Frank, M.D., President
Jerome J. Sievers, M.D., Vice President
Ralph Bookman, M.D., Secretary-Treasurer

CUBAN ALLERGY SOCIETY

New officers and directors of the Cuban Society of Allergy for 1957 are:

President: Dr. José Cadrecha Alvarez
Vice President: Dr. José M. Quintero Fossas
Secretary: Dr. Julio de Los Santos
Treasurer: Dr. Javier Fernández de Castro
Directors: Dr. Gonzalo Estrada de la Riva, Dr. Margarita Lorigado, Dr. José J. Pedrera

CALIFORNIA SOCIETY OF ALLERGY

The California Society of Allergy elected the following officers for 1957-58:

President: Willard S. Small, M.D., Pasadena
Vice President: William J. Kerr, Jr., M.D., San Rafael
Secretary: Albert Rowe, Jr., M.D., Oakland

BOOK REVIEWS

THE LUNG AS A MIRROR OF SYSTEMIC DISEASE. Eli H. Rubin. 288 pages including index. Springfield, Illinois: Charles C Thomas, 1956. $12.50.

In his preface, the author writes that this volume is "a segment of medicine with emphasis on disseminated diseases which may be associated with pulmonary lesions as part of the basic disturbance." He therefore gives as much time to description of the eighty diseases included, each as a whole, as he does to the pulmonary lesion itself. He ends by saying that he hopes "that this book will alert the physician to the wealth of information obtainable in a chest x-ray provided the latter is viewed in broad prospective."

Dr. Rubin stresses the fact that there are occasions when the physical examination is more informative than the chest x-ray findings and the history superior to both. But, in the diagnosis of obscure systemic disease with pulmonary lesions of the type he has selected for description, physical signs may be lacking and it may not be possible to demonstrate organ or tissue involvement outside of the chest.

Since approximately 18,000,000 people, or about one-tenth of our population, consult physicians annually, the opportunity to request a chest x-ray is frequently present. Its proper interpretation may save the patient much future suffering.

What are the disorders a routine chest x-ray may help uncover?

The metabolic diseases include hypertrophic pulmonary arthropathy, diabetes, cystic fibrosis of the pancreas, the various forms of histiocytosis, amyloidosis and pulmonary metastatic calcification. Among the blood diseases are sickle cell anemia, pulmonary hemosiderosis, polycythemia, leukemia, myelomatosis and infectious mononucleosis. Then there are the groups of the collagen diseases and of the skin and mucous membranes. The pulmonary manifestations of abdominal, cardiovascular and metastatic conditions will be ever present in every physician's mind.

The last seventy pages are given to general considerations including the changing scene in diagnosis, signs and symptoms, the physical examination of the chest, anatomic and technical considerations of the chest x-ray, pitfalls in roentgen diagnosis and laboratory and exploratory aids. There are ninety-two excellent illustrations and eleven tables.

Dr. Rubin writes well and with a fresh point of view. He brings (to what is often a dull subject) enthusiasm which shines through the words with which he describes the systemic disorders that may be mirrored in the lungs.

His students at the Albert Einstein College of Medicine must like him.

ALLERGIC DERMATOSES DUE TO PHYSICAL AGENTS. Edited by Rudolf L. Baer, M.D. (This material was published in American Practitioner and Digest of Treatment, August, 1956.) 110 pages with index. New York: New York University Press, 1956 (distributed, J. B. Lippincott Company). Price $3.00.

The editor states in his preface that a sharp delineation between allergic and nonallergic hypersensitivities to physical agents is not always possible. Dr. Baer says, "An allergic basis may be established clearly for some of these hypersensitivities, while in others proof of a specific immunologic mechanism may be weak or entirely lacking. The present text does not claim to resolve the many existing doubts in this field, nor does it cover the existing knowledge in a complete and an exhaustive manner. Rather, it is hoped that it will serve as an outline of what is known and, equally important, of the tremendous gaps in our knowledge of this exceptionally interesting but relatively unexplored segment of immunology."

Dr. Allan L. Lorincz ably discusses hypersensitivity to trauma. Eczematous and

polymorphous hypersensitivity to light is summarized by Dr. Herman V. Allington, while urticarial hypersensitivity to light is discussed by Stephan Epstein. Hypersensitivity to heat and cold are successively described by Dr. Otis F. Jillson and by Drs. Sylvia F. Griem and Stephen Rothman.

The material presented in this booklet should be familiar to all allergists. Those interested in obtaining detailed knowledge of this subject will find the bibliographies attached to each chapter unusually complete.

OCCUPATIONAL DISEASES OF THE SKIN. Louis Schwartz, M.D.; Louis Tulipan, M.D.; and Donald J. Birmingham, M.D. Third Edition. 981 pages. Philadelphia: Lea & Febiger, 1957. Price $18.00.

Allergy being the specialty that it is, every allergist will see patients who are suffering from contact dermatitis. The previous two editions of this text (first published in 1939) have stood the test of time as the source books for knowledge of the dermatidites which occur in more than 100 occupations. The present edition includes special chapters on "Occupational Marks" by Dr. Francesco Ronchese, on "Skin Hazards from Radiation in Atomic Industry, Medicine and Warfare" by Dr. W. D. Norwood, and on "Skin Hazards from Surface Active Agents" by Dr. Anthony M. Schwartz.

The book has been shortened by the omission of bibliographic references to material published before 1943 which can easily be obtained from the previous editions.

Compensation for and medical-legal aspects of occupational dermatitis are discussed from the point of view of the testifying physician, who is given the information he needs to withstand strict cross-examination.

The chapter dealing with irritant plants and woods is unusually complete. Listed alphabetically are the more than 1,000 substances needed for patch-testing and the test concentrations used for each as compiled by Dr. Adolph Rostenberg, Jr., and Dr. Marion B. Sultzberger, as added to by Dr. Joseph Goodman. Listed separately are those chemicals which are known to be primary skin irritants and sensitizers.

The authors have not hesitated to draw on foreign as well as American literature to make the book encyclopedic.

LECTURES IN IMMUNOCHEMISTRY. Michael Heidelberger. 150 pages with index. New York: Academic Press, 1956. Price $4.00.

Dr. Heidelberger and his students have been responsible for isolating antibodies and devising techniques by means of which they can be studied by quantitative methods. The book consists of six lectures given in Tokyo late in 1955. The author reviews his contributions from the time that he and the late O. T. Avery isolated the capsular polysaccharides of the pneumococcus, about thirty-five years ago. Any allergist who wishes to familiarize himself with the history and present state of this aspect of immunochemistry will find the effort well worth while.